11-30-01

FORM PTO-1390 (REV 10-95) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (If known, see 37 CFR 1.5)
0380-P02746US0	09/980217

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB00/02072	30 May 2000	28 May 1999

TITLE OF INVENTION
POLYKETIDES AND THEIR SYNTHESIS

APPLICANT(S) FOR DO/EO/US
LEADLAY, Peter Francis et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendemnts has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information:

    Copy of Form PCT/IB/308

JC10 Rec'd PCT/PTO 28 NOV 2001

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/980217	PCT/GB00/02072	0380-P02746US0

17. [X] The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):

Search Report has been prepared by the EPO or JPO . . . .

International preliminary examination fee paid to USPTO (37 CFR 1.482) . . . .

No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) . . . .

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO . . . .

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) . . . .

				CALCULATIONS	PTO USE ONLY
ENTER APPROPRIATE BASIC FEE AMOUNT =				$ 890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				$ 130.00	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	47 -20 =	17	X 18.00	$ 306.00	
Independent claims	16 -3 =	13	X 84.00	$ 1,092.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ 280.00	$ 0.00	
TOTAL OF ABOVE CALCULATIONS =				$ 2,418.00	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).				$ 1,209.00	
SUBTOTAL =				$ 1,209.00	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$ 0.00	
TOTAL NATIONAL FEE =				$ 1,209.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 0.00	
TOTAL FEES ENCLOSED =				$ 1,209.00	
				Amount to be: refunded	$
				charged	$

a. [X] A check in the amount of $ 1,209.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. ________ in the amount of $________ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 04-1406. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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THE UNITED STATES PATENT AND TRADEMARK OFFICE

United States Serial No.	:	Not yet assigned
International Application No.	:	PCT/GB00/02072
International Filing Date	:	30 May 2000
Inventor(s)	:	Peter Francis Leadlay et al.
Title	:	POLYKETIDES AND THEIR SYNTHESIS

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PRELIMINARY AMENDMENT

Dear Sir:

Before calculation of the filing fee, please amend the claims of the above-referenced patent application, as follows:

In the Claims:

Please amend claims 1, 8-15, 17-23, 26, 29, 33, 35, 37, 38 and 42 as follows:

1. (Amended) A DNA sequence which is selected from the group consisting of (a) at least part of the sequence set out in the appended sequence listing; and (b) a variant of a sequence (a) which encodes a polypeptide which is at least 80%, identical with the corresponding peptide as set out in table II; provided that it is not a sequence encoding all or part of the polypeptide consisting of amino acids 1-920 encoded by *mon AI* as set out in table II.

8. (Amended) A DNA sequence according to claim 1 encoding any one or more of the domains as set out in Table I or a variant or part thereof.

9. (Amended) A DNA sequence according to claim 1 which has a length of at least 30 bases.

10. (Amended) A recombinant cloning or expression vector comprising a DNA sequence according to claim 1.

11. (Amended) A transformant host cell which has been transformed to contain a DNA sequence according to claim 1 and which is capable of expressing a corresponding polypeptide.

12. (Amended) A hybridisation probe which is a DNA sequence according to claim 1.

13. (Amended) A method of detecting a PKS cluster comprising using a probe according to claim 12 to detect a PKS cluster, optionally followed by isolation of the detected cluster.

14. (Amended) A method of detecting genes comprising using a probe according to claim 12 which encodes at least part of a polypeptide having a known function to detect genes encoding polypeptides having analogous function.

15. (Amended) A method according to claim 14 wherein the polypeptide of known function is AT of module 5 or the regulatory protein encoded by *mon RI*.

17. (Amended) A method of detecting the presence of a gene cluster which governs the synthesis of a polyether, which comprises using a probe according to claim 16, and optionally isolating a gene cluster detected thereby.

18. (Amended) A method of detecting a gene comprising using a probe according to claim 12 which comprise a polynucleotide which binds specifically to a gene responsible for levels of activity of the monensin gene cluster, for detecting an

analogous gene in a gene cluster for biosynthesis of another polyketide, optionally followed by a step of manipulating the gene detected thereby to alter the level of expression of said other polyketide.

19. (Amended) A method according to claim 18 wherein the gene is a regulatory gene, resistance gene or thioesterase gene.

20. (Amended) A method of expressing a heterologous gene in *S. cinnamonesis* comprising inserting said gene so that it is expressed under the control of the *mon RI* gene or variant and a monensin promoter.

21. (Amended) A method of expressing a polyketide other than monensin which includes using a portion of the monensin gene cluster encoding a polypeptide having chain terminating activity, comprising at least one of *mon AIX* and *mon AX* or a mutant, allele or other variant thereof encoding a polypeptide having chain terminating activity, to effect chain release of said polyketide other than monensin.

22. (Amended) A method of synthesising a polyketide other than monensin which includes using a portion of the monensin gene cluster encoding a polypeptide having carbon-carbon double bond isomerase activity comprising at least one of

mon BI and *mon BII* or a mutant, allele or other variant thereof having isomerase activity to provide a desired stereochemical outcome in the synthesis of said polyketide other than monensin.

23. (Amended) A polypeptide encoded by a portion of the monensin gene cluster, comprising at least one portion selected from *mon BI* and *mon BII* or a mutant, allele or other variant thereof, having carbon-carbon double bond isomerase activity, or at least one of *mon AIX* and *mon AX* or a mutant, allele or other variant thereof having chain terminating activity.

26. (Amended) A method for the biosynthesis of a polyketide other than monensin which comprises using a portion of the monensin gene cluster encoding a peptide having epoxidase or cyclase activity, to provide a said activity in the biosynthesis of said polyketide other than monensin.

29. (Amended) A process according to claim 27 wherein the starter unit also includes an AT_q domain derived from an AT domain which is naturally associated with the KS domain.

33. (Amended) A DNA sequence according to claim 30 wherein said loading module is adapted to load a starter unit other than a starter unit normally received by the adjacent extension module.

35. (Amended) A polyketide synthase encoded by the DNA sequence of claim 30.

37. (Amended) A vector containing a DNA sequence of claim 30.

38. (Amended) A transformant cell transformed to contain a DNA sequence of claim 30.

42. (Amended) A method of producing monensin comprising culturing the organism of claim 41.

Please add new claims 46 and 47 as follows:

46. (New) A DNA sequence according to claim 1 which is a variant of a sequence (a) which encodes a peptide which is at least 90% identical with the corresponding peptide as set out in table II.

47. (New) A DNA sequence according to claim 1 which has a length of at least 60 bases.

REMARKS

The purpose of this Preliminary Amendment is to eliminate multiple claims dependencies, revise claims which, due to their form, do not comply with current U.S. Patent and Trademark Office practice, and to present additional claims directed to preferred embodiments of the invention.

The foregoing amendments do not introduce new matter into the present application, and, therefore, should be entered without objection.

Early and favorable consideration of the present application is respectfully requested.

Respectfully submitted,

Patrick J. Hagan

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Attorney for Applicant

PJH:ksk

MARKED-UP COPY OF THE CLAIMS

1. (Amended) A DNA sequence which is selected from the group consisting of (a) at least part of the sequence set out in the appended sequence listing; [or] and (b) a variant of a sequence (a) which encodes a polypeptide which is at least 80%, [preferably at least 90%], identical with the corresponding peptide as set out in table II; provided that it is not a sequence encoding all or part of the polypeptide consisting of amino acids 1-920 encoded by *mon AI* as set out in table II.

8. (Amended) A DNA sequence according to [any preceding] claim 1 encoding any one or more of the domains as set out in Table I or a variant or part thereof.

9. (Amended) A DNA sequence according to [any preceding] claim 1 which has a length of at least 30[, preferably at least 60,] bases.

10. (Amended) A recombinant cloning or expression vector comprising a DNA sequence according to [any preceding] claim 1.

11. (Amended) A transformant host cell which has been transformed to contain a DNA sequence according to [any of claims 1-9] claim 1 and which is capable of expressing a corresponding polypeptide.

12. (Amended) A hybridisation probe which is a DNA sequence according to [any of claims 1-9] claim 1.

13. (Amended) A method of detecting a PKS cluster comprising using [Use of] a probe according to claim 12 to detect a PKS cluster, optionally followed by isolation of the detected cluster.

14. (Amended) A method of detecting genes comprising using [Use of] a probe according to claim 12 which encodes at least part of a polypeptide having a known function to detect genes encoding polypeptides having analogous function.

15. (Amended) A method [Use] according to claim 14 wherein the polypeptide of known function is AT of module 5 or the regulatory protein encoded by *mon RI*.

17. (Amended) [Use of a probe according to claim 16 in a] A method of detecting the presence of a gene cluster which governs the synthesis of a polyether, which comprises using a probe according to claim 16, and optionally isolating a gene cluster detected thereby.

18. (Amended) [Use of] A method of detecting a gene comprising using a probe according to claim 12 which comprise a polynucleotide which binds specifically to a gene

responsible for levels of activity of the monensin gene cluster, [in a method of] for detecting an analogous gene in a gene cluster for biosynthesis of another polyketide, optionally followed by a step of manipulating the gene detected thereby to alter the level of expression of said other polyketide.

19. (Amended) A method [Use] according to claim 18 wherein the gene is a regulatory gene, resistance gene or thioesterase gene.

20. (Amended) A method of expressing a heterologous gene in *S. cinnamonesis* comprising inserting said gene so that it is expressed under the control [Use] of the *mon RI* gene or variant and a monensin promoter [to control expression of a heterologous gene in *S. cinnamonensis*].

21. (Amended) A method of expressing a polyketide other than monensin which includes using [Use of] a portion of the monensin gene cluster encoding a polypeptide having chain terminating activity, [preferably] comprising at least one of *mon AIX* and *mon AX* or a mutant, allele or other variant thereof encoding a polypeptide having chain terminating activity, to effect chain release of [a peptide] said polyketide other than monensin.

22. (Amended) A method of synthesising a polyketide other than monensin which includes using [Use of] a portion of the monensin gene cluster encoding a polypeptide having carbon-carbon double bond isomerase activity[, preferably] comprising at least one of *mon BI* and *mon BII* or a mutant, allele or other variant thereof having isomerase activity to provide a desired stereochemical outcome in the synthesis of [a] said polyketide other than monensin.

23. (Amended) A polypeptide encoded by a portion of the monensin gene cluster, [preferably] comprising at least one [of] portion selected from *mon BI* and *mon BII* or a mutant, allele or other variant thereof, having carbon-carbon double bond isomerase activity, or at least one of *mon AIX* and *mon AX* or a mutant, allele or other variant thereof having chain terminating activity.

26. (Amended) A method for the biosynthesis of a polyketide other than monensin which comprises using [Use of] a portion of the monensin gene cluster encoding a peptide having epoxidase or cyclase activity, [preferably comprising *mon CI* or *mon CII* or a mutant, allele or other variant thereof encoding a polypeptide having epoxidase or cyclase activity] to provide a said activity in the biosynthesis of [a polypeptide] said polyketide other than monensin.

29. (Amended) A process according to claim 27 [or claim 28] wherein the starter unit also includes an AT_q domain derived from an AT domain which is naturally associated with the KS domain.

33. (Amended) A DNA sequence according to claim 30[, 31 or 32] wherein said loading module is adapted to load a starter unit other than a starter unit normally received by the adjacent extension module.

35. (Amended) A polyketide synthase encoded by the DNA sequence of [any of claims 30-34] claim 30.

37. (Amended) A vector containing a DNA sequence of [any of claims 30-34] claim 30.

38. (Amended) A transformant cell transformed to contain a DNA sequence of [any of claims 30-34] claim 30.

42. (Amended) A method of producing monensin comprising culturing the organism of claim 41 [and/or an organism produced by the method of claim 39 or claim 40].

POLYKETIDES AND THEIR SYNTHESIS

The present invention relates to processes and materials (including enzyme systems, nucleic acids, vectors and cultures) for preparing polyketides, particularly polyethers but including polyenes, macrolides and other polyketides by recombinant synthesis, and to the polyketides so produced, particularly novel polyketides. (N.B the term "polyketide" is being used in its conventional sense to include structures notionally derived by the reduction and/or other processing or modification of one or more Ketide units). Furthermore the invention provides the entire nucleic acid sequence of the biosynthetic gene cluster that governs the production of the ionophoric antibiotic polyether polyketide monensin in *Streptomyces cinnamonensis*, and the use of all or part of the cloned DNA first, in the specific detection of other polyether biosynthetic gene clusters; secondly in the engineering of mutant strains of *S. cinnamonensis* and of other actinomycetes which are suitable host strains for the high level production of novel recombinant polyketides; and thirdly in the provision of recombinant biosynthetic genes which lead to such novel polyketide products.

Polyketides are a large and structurally diverse

class of natural products that includes many compounds possessing antibiotic or other pharmacological properties, such as erythromycin, tetracyclines, rapamycin, avermectin, monensin, epothilones and FK506. In particular, polyketides are abundantly produced by *Streptomyces* and related actinomycete bacteria. They are synthesised by the repeated stepwise condensation of acylthioesters in a manner analogous to that of fatty acid biosynthesis. The greater structural diversity found among natural polyketides arises from the selection of (usually) acetate or propionate as "starter" or "extender" units; and from the differing degree of processing of the β-keto group observed after each condensation. Examples of processing steps include reduction to β-hydroxyacyl-, reduction followed by dehydration to 2-enoyl-, and complete reduction to the saturated acylthioester. The stereochemical outcome of these processing steps is also specified for each cycle of chain extension. In addition, the biosynthetic pathways to many polyketides involve additional enzyme-catalysed modifications which may include: methylation by O- and C-methyltransferases, hydroxylation by cytochrome P450 enzymes, other oxidation or reduction processes, and the biosynthesis and attachment of novel sugars and/or deoxy sugars.

The biosynthesis of polyketides is initiated by a group of chain-forming enzymes known as polyketide synthases. Two classes of polyketide synthase (PKS) have been described in actinomycetes. One class, named Type I PKSs, represented by the PKSs for the macrolides erythromycin, oleandomycin, avermectin and rapamycin, consists of a different set or "module" of enzymes for each cycle of polyketide chain extension. (For examples see Cortés, J. *et al.* Nature (1990) 348:176-178; Donadio, S. *et al.* Science (1991) 252:675-679; Swan, D.G. *et al.* Mol. Gen. Genet. (1994) 242:358-362; MacNeil, D.J. *et al.* Gene (1992) 115:119-125; Schwecke, T. *et al.* Proc. Natl. Acad. Sci. USA (1995) 92:7839-7843.)

The term "extension module" as used herein refers to the set of contiguous domains, from a β-ketoacyl-ACP synthase ("KS") domain to the next acyl carrier protein ("ACP") domain, which accomplishes one cycle of polyketide chain extension. The term "loading module" is used to refer to any group of contiguous domains which accomplishes the loading of the starter unit onto the PKS and thus renders it available to the KS domain of the first extension module. The length of polyketide formed has been altered, in the case of erythromycin biosynthesis, by specific relocation using genetic engineering of the enzymatic domain of the erythromycin-

producing PKS that contains the chain releasing thioesterase/cyclase activity (Cortés J. *et al.* Science (1995) 268:1487-1489; Kao, C.M. *et al.* J. Am. Chem. Soc. (1995) 117:9105-9106).

In-frame deletion of the DNA encoding part of the ketoreductase domain in module 5 of the erythromycin-producing PKS (also known as 6-deoxyerythronolide B synthase, DEBS) has been shown to lead to the formation of erythromycin analogues 5,6-dideoxy-3-α-mycarosyl-5-oxoerythronolide B, 5,6-dideoxy-5-oxoerythronolide B and 5,6-dideoxy,6-β-epoxy-5-oxoerythronolide B (Donadio, S. *et al.* Science (1991) 252:675-679). Likewise, alteration of active site residues in the enoylreductase domain of module 4 in DEBS, by genetic engineering of the corresponding PKS-encoding DNA and its introduction into *Saccharopolyspora erythraea*, led to the production of 6,7-anhydroerythromycin C (Donadio, S. *et al.* Proc. Natl. Acad. Sci. USA (1993) 90:7119-7123).

International Patent Application number WO 93/13663 describes additional types of genetic manipulation of the DEBS genes that are capable of producing altered polyketides. However many such attempts are reported to have been unproductive (Hutchinson, C.R. and Fujii, I. Annu. Rev. Microbiol. (1995) 49:201-238, at p. 231). The complete DNA sequence of the genes from *Streptomyces*

hygroscopicus that encode the modular Type I PKS governing the biosynthesis of the macrocyclic immunosuppressant polyketide rapamycin has been disclosed (Schwecke, T. *et al.* (1995) Proc. Natl. Acad. Sci. USA 92:7839-7843). The DNA sequence is deposited in the EMBL/Genbank Database under the accession number X86780.

WO 98/01546 discloses that a PKS gene assembly (particularly of Type I) encodes a loading module which is followed by at least one extension module. The first open reading frame encodes the first multi-enzyme or cassette (DEBS1) which consists of three modules: the loading module (ery-load) and two extension modules (modules 1 and 2). The loading module comprises an acyltransferase and an acyl carrier protein. This may be contrasted with Figure 1 of WO 93/13663 (referred to above). This shows ORF1 as only two modules, the first of which is in fact both the loading module and the first extension module.

WO 98/01546 describes in general terms the production of a hybrid PKS gene assembly comprising a loading module and at least one extension module. It also describes (see also Marsden, A.F.A. *et al.* Science (1998) 279:199-202) construction of a hybrid PKS gene assembly by grafting the wide-specificity loading module for the avermectin-producing polyketide synthase onto the first

multi-enzyme component (DEBS1) for the erythromycin PKS in place of the normal loading module. Certain novel polyketides can be prepared using the hybrid PKS gene assembly, as described for example in WO 98/01571.

WO 98/01546 further describes the construction of a hybrid PKS gene assembly by grafting the loading module for the rapamycin-producing polyketide synthase onto the first multi-enzyme component (DEBS1) for the erythromycin PKS in place of the normal loading module. The loading module of the rapamycin PKS differs from the loading modules of DEBS and the avermectin PKS in that it comprises a CoA ligase domain, an enoylreductase ("ER") domain and an ACP, so that suitable organic acids including the natural starter unit 3,4-dihydroxycyclohexane carboxylic acid may be activated *in situ* on the PKS loading domain and, with or without reduction by the ER domain, transferred to the ACP for intramolecular loading of the KS of extension module 1 (Schwecke, T. *et al.* Proc. Natl. Acad. Sci. USA (1995) 92:7839-7843). WO 98/51695 and WO 98/49315 describe additional types of genetic manipulation of the DEBS genes that are capable of producing altered polyketides.

The second class of PKS, named Type II PKSs, is represented by the synthases for aromatic compounds. Type II PKSs contain only a single set of enzymatic activities

for chain extension and these are re-used as appropriate in successive cycles (Bibb, M.J. *et al.* EMBO J. (1989) 8:2727-2736; Sherman, D.H. *et al.* EMBO J. (1989) 8:2717-2725; Fernandez-Moreno, M.A. *et al.* J. Biol. Chem. (1992) 267:19278-19290). The "extender" units for the Type II PKSs are usually acetate units, and the presence of specific cyclases dictates the preferred pathway for cyclisation of the completed chain into an aromatic product (Hutchinson, C.R. and Fujii, I. Ann. Rev. Microbiol. (1995) 49:201-238). Hybrid polyketides have been obtained by the introduction of cloned Type II PKS gene-containing DNA into another strain containing a different Type II PKS gene cluster, for example by introduction of DNA derived from the gene cluster for actinorhodin, a blue-pigmented polyketide from *Streptomyces coelicolor*, into an anthraquinone polyketide-producing strain of *Streptomyces galileus* (Bartel, P.L. *et al.* J. Bacteriol. (1990) 172:4816-4826).

The minimal number of domains required for polyketide chain extension on a Type II PKS when expressed in a *Streptomyces coelicolor* host cell (the "minimal PKS") has been defined for example in WO 95/08548 as containing the following three polypeptides which are products of the *actI* genes: firstly KS; secondly a polypeptide termed the CLF with end-to-end

amino acid sequence similarity to the KS but in which the essential active site residue of the KS, namely a cysteine residue, is substituted either by a glutamine residue or, in the case of the PKS for a spore pigment such as the *whiE* gene product (Davis, N.K. and Chater, K.F. Mol. Microbiol. (1990) 4:1679-1691) by a glutamic acid residue; and finally an ACP. The CLF has been stated (for example in WO 95/08548) to be a factor that determines the chain length of the polyketide chain that is produced by the minimal PKS. However it has been found (Shen, B. *et al.* J. Am. Chem. Soc. (1995) 117:6811-6821) that when the CLF for the octaketide actinorhodin is used to replace the CLF for the decaketide tetracenomycin in host cells of *Streptomyces glaucescens*, the polyketide product is not found to be altered from a decaketide to an octaketide, so the exact role of the CLF remains unclear. An alternative nomenclature has been proposed in which KS is designated KSα and CLF is designated KSβ, to reflect this lack of knowledge (Meurer, G. *et al.* Chemistry & Biology (1997) 4:433-443). The mechanism by which acetate starter units and acetate extender units are loaded onto the Type II PKS is not known, but it is speculated that the malonyl-CoA: ACP acyltransferase of the fatty acid synthase of the host cell can fulfil the same function for the Type II PKS (Revill, W.P. *et al.* J.

Bacteriol. (1995) 177:3946-3952).

WO 95/08548 describes the replacement of actinorhodin PKS genes by heterologous DNA from other Type II PKS gene clusters, to obtain hybrid polyketides. It also describes the construction of a strain of *Streptomyces coelicolor* which substantially lacks the native gene cluster for actinorhodin, and the use in that strain of a plasmid vector pRM5 derived from the low-copy number vector SCP2* isolated from *Streptomyces coelicolor* (Bibb, M.J. and Hopwood, D.A. J. Gen. Microbiol. (1981) 126:427-442) and in which heterologous PKS-encoding DNA may be expressed under the control of the divergent *actI/actIII* promoter region of the actinorhodin gene cluster (Fernandez-Moreno, M.A. *et al.* J. Biol. Chem. (1992) 267:19278-19290). The plasmid pRM5 also contains DNA from the actinorhodin biosynthetic gene cluster encoding the gene for a specific activator protein, ActII-orf4. The ActII-orf4 protein is required for transcription of the genes placed under the control of the *actI/actIII* bidirectional promoter and activates gene expression during the transition from growth to stationary phase in the vegetative mycelium (Hallam, S.E. *et al.* Gene (1988) 74:305-320).

Type II clusters in *Streptomyces* are known to be activated by pathway-specific activator genes (Narva,

K.E. and Feitelson, J.S. J. Bacteriol. (1990) 172:326-333; Stutzman-Engwall, K.J. *et al.* J. Bacteriol. (1992) 174:144-154; Fernandez-Moreno, M.A. *et al.* Cell (1991) 66:769-780; Takano, E. *et al.* Mol. Microbiol. (1992) 6:2797-2804; Gramajo, H.C. *et al.* Mol. Microbiol. (1993) 7:837-845). The DnrI gene product complements a mutation in the *actII*-orf4 gene of *S. coelicolor*, implying that DnrI and ActII-orf4 proteins act on similar targets. A gene (*srmR*) has been described (EP 0 524 832 A2) that is located near the Type I PKS gene cluster for the macrolide polyketide spiramycin. This gene specifically activates the production of the macrolide antibiotic spiramycin, but no other examples have been found of such a gene. Also, no homologues of the ActII-orf4/DnrI/RedD family of activators have been described that act on Type I PKS genes. WO 98/01546 describes the use of the ActII-orf4 family of activators in conjunction with their cognate promoters (e.g actII-orf4 with the *actI* promoter) in a heterologous actinomycete to obtain high level expression of recombinant Type I polyketide synthase genes.

Although large numbers of therapeutically important polyketides have been identified, there remains a need to obtain novel polyketides that have enhanced properties or possess completely novel bioactivity. The complex

polyketides produced by Type I PKSs are particularly valuable, in that they include compounds with known utility as anthelminthics, insecticides, immunosuppressants, antifungal agents or antibacterial agents. Because of their structural complexity, such novel polyketides are not readily obtainable by total chemical synthesis, nor by chemical modifications of known polyketides.

There is also a need to develop reliable and specific ways of deploying individual genes and portions of genes in practice so that all, or a large fraction, of hybrid PKS genes that are constructed, are viable and produce the desired polyketide product. This includes the development of advantageous host strains for expression of such genes. For example many polyketides are rendered bioactive by the action of further enzymes other than the polyketide synthase, and host strains that contain and are able to express the genes for such enzymes are particularly convenient for the efficient synthesis of the bioactive material. In those cases where the construction of a known or a novel polyketide requires specialised precursors, host strains containing and able to express the genes for key enzymes that enhance the production of such specialised precursors are equally valuable and desirable. There is also a need to develop

rational methods of increasing the expression level of all the genes required for production of a specific polyketide. Clearly also a host cell which is advantageous for the above reasons, and/or because of other favourable characteristics including but not limited to its speed of growth, excellent handling characteristics in fermentation, and ease of transformation with DNA by various techniques, can be made even more favourable by the cloning into that cell of such auxiliary genes for polyketide modification, or gene activation, or post-translational modification, or precursor supply.

The DNA sequences have been disclosed for several Type I PKS gene clusters that govern the production of 16-membered macrolide polyketides, including the tylosin PKS from *Streptomyces fradiae* (application EP 0 791 655 A2), the niddamycin PKS from *Streptomyces caelestis* (Kavakas, S.J. *et al.* J. Bacteriol. (1997) 179:7515-7522) and the spiramycin PKS from *Streptomyces ambofaciens* (application EP 0791 655 A2). DNA sequences have also been disclosed for Type I PKS gene clusters that govern the production of further complex polyketides, for example rifamycin from *Amycolatopsis mediterranei* (WO 98/07868), and soraphen from *Sorangium cellulosum* (US

5716849), but so far no DNA sequence has been disclosed for one of the most widespread and important classes of complex polyketides, the polyethers.

Polyethers form an important group of complex polyketide antibiotics (Westley, J.W. in "Antibiotics IV. Biosynthesis" (Corcoran, J.W. Ed.), Springer-Verlag, New York (1981) p. 41-73). They are polyoxygenated carboxylic acids which act as selective ionophores transporting cations across the cell membrane of target cells and thereby causing depolarisation and cell death. Certain polyethers including monensin, lasalocid and tetronasin are in widespread use in animal husbandry as coccidiostats (principally targetted against *Eimeria spp.*) and as growth promoters. Polyethers have also been reported to be active *in vitro* and *in vivo* against the malarial parasite *Plasmodium falciparum* (Gumila, C. *et al.* Antimicrobial Agents and Chemotherapy (1997) 41: 523-529).

Polyethers contain multiple asymmetric centres and are characterised by the presence of tetrahydrofuran and tetrahydropyran rings, producing a characteristic shape which is non-polar on its outer surface and therefore well adapted for transport of material across bacterial membranes; and provides on its inner surface polar coordinating ligands for a centrally-bound metal ion. In

addition to tetrahydrofuran and tetrahydropyran rings, other groups which are often present include spiroketal, dispiroketal, and substituted benzoic acid moieties and occasionally other groups for example a tetronic acid or a 6-membered carbocyclic ring

Monensins A and B are produced by the actinomycete *Streptomyces cinnamonensis*. Their structures are shown in Figure 1. Monensin B differs from monensin A only in the presence of a methyl sidechain at C-16 rather than an ethyl sidechain. Monensin selectively binds and transports sodium ions. In addition to its antibacterial and antifungal properties monensin has some activity against protozoal parasites such as the malarial parasite *Plasmodium falciparum*. Although the structures of polyethers differ significantly from those of other complex polyketides such as the polyhydroxylated and polyene macrolides, their biosynthesis appears to take place by a metabolic pathway which has many common elements. Thus experiments using carbon 14-labelled precursors have shown that monensin A is synthesised from five acetate, one butyrate and seven propionate units (Day, L.E. *et al.* Antimicrob. Agents Chemother. (1973) 4:410-414). Similarly experiments using precursors doubly-labelled with carbon-13 and oxygen-18 have shown that oxygens (O)1, (O)3, (O)4, (O)5, (O)6 and (O)10 of

monensin arise from the carboxylate oxygens of either propionate or acetate, while growth in the presence of oxygen-18 oxygen gas demonstrated that the three remaining ether oxygens (O)7, (O)8 and (O)9 are derived from molecular oxygen (Cane, D.E. *et al.*, J. Am. Chem. Soc. (1981) 103:5962-5965; Cane, D.E. *et al.* J. Am. Chem. Soc. (1982) 104:7274 - 7281; Ajaz, A.A. and Robinson, J.A. J. Chem. Soc. Chem. Commun. (1983) 12:679-680). These findings have been rationalised by proposing that the biosynthesis of monensin proceeds via an acyclic triene intermediate (1) in which the geometry of all three carbon-carbon double bonds is E (entgegen) rather than Z (zusammen). The triene is then proposed to be subject to epoxidation to a tri-epoxide (2) and then ring opening is proposed to occur with concomitant sequential formation of the five ether rings as shown in Figure 2A. Such a biosynthetic pathway, first mooted by Westley in 1974 (Westley J.W. *et al.*, J. Antibiot. (1974) 27:597-604) accounts for the observed stereochemistry at the multiple asymmetric centres in monensin, (Cane, D.E. *et al.* J. Am. Chem. Soc. (1982) 104:7274-7281; Sood, G.R. *et al.* J. Chem. Soc. Chem. Commun. (1984) 21:1421-1424) and analogous schemes can be used to account for the biosynthesis of other known polyethers. such as lasalocid A (Hutchinson C.R. *et al.*, J. Am. Chem. Soc. (1981)

103:5953-5956), tetronasin (ICI 139603) (Demetriadou, A.K. *et al.* J. Chem. Soc. Chem. Commun. (1985) 7:408-410) and narasin (Spavold, Z. *et al.* Tetrahedron Letters (1986) 27:3299-3302). The hydroxylation at C-26 and the introduction of an O-methyl group on oxygen 3-are proposed to occur as late steps in the biosynthesis, after formation of the polyether structure.

Unfortunately key aspects of the biosynthetic scheme shown in Figure 2A have so far eluded experimental confirmation. No biosynthetic intermediates have been isolated from mutants of *S. cinnamonensis* that are blocked in early stages of monensin production. 26-deoxymonensin A has been isolated from a *S. cinnamonensis* mutant partially blocked in monensin production (Ashworth, D.M. *et al.* J. Antibiot. (1989) 42:1088-1099) and 3-O-demethylmonensins A and B have been recovered as minor components from the fermentation broth of a monensin-producing strain (Pospisil, S. *et al.* J. Antibiot. (1987) 40:555-557). When fed to cells of *S. cinnamonensis* in radio-labelled form, neither 26-deoxymonensin A, nor 3-O-demethylmonensin A, nor 3-O-demethyl, 26-deoxymonensin A were significantly incorporated into monensin A (Ashworth, D.M. *et al.* J. Antibiot. (1989) 42:1088-1099), either because they are actively excluded or because these modifications in fact

occur earlier in the biosynthetic pathway so that these metabolites are shunt products not readily converted into the final antibiotic by the respective hydroxylase or methyltransferase. Similarly, the putative all (E)-triene precursor (1) has been synthesised and shown not to become incorporated into monensin when fed to growing cells of *S. cinnamonensis* (Holmes, D.S. *et al.* Helv. Chim. Acta (1990) 73:239-259). An alternative pathway has been proposed, as shown in Fig 2B, based on the transition-metal-mediated oxidation of 1,5-dienes (Walba, D.M. and Edwards, P.D. Tetrahedron Lett. (1980) 21:3531-3534). The triene intermediate (4) would different from that of Figure 2A (1) only in that each carbon-carbon double bond would have the (Z)-configuration (Townsend, C.A. and Basak, A. Tetrahedron (1991) 47:2591-2602) and not the (E)- configuration.

The genetic basis of secondary metabolite biosynthesis essentially exists in the genes which code for the individual biosynthetic enzymes and in the regulatory elements which control the expression of the biosynthetic genes. The genes encoding biosynthesis of polyketides in actinomycetes have hitherto been found as clusters of adjacent genes, ranging in size from 20 kilobasepairs (kbp) to over 100 kbp. The clusters often contain specific regulatory genes and genes

conferring resistance of the producing strain to its own antibiotic.

In various of its aspects the invention provides the following:-

(1) a DNA sequence encoding at least one peptide necessary for the biosynthesis of monensin, preferably comprising one or more of the following genes: *mon BI, mon BII, mon CI, mon CII, mon H, mon RI, mon RII, mon T, mon AIX* and *mon AX* as depicted in the appended sequence data or an allele or mutation thereof;

(2) a DNA sequence according to the first aspect comprising all of the genes listed therein or an allele or mutation thereof;

(3) a DNA sequence according to the first aspect comprising the complete monensin gene cluster;

(4) a DNA sequence coding for one or more of the peptides set out below, said peptide having the amino acid sequence as set out in the appended sequence data or being a variant thereof having the specified activity:

peptide	activity
mon CII	epoxyhydrolase/cyclase
mon E	S-adenosylmethionine-dependent methyltransferase
mon T	monensin resistance gene
mon RII	repressor protein
mon AIX	thioesterase

mon AI	polyketide synthase multienzyme
mon AII	polyketide synthase multienzyme
mon AIII	polyketide synthase multienzyme
mon AIV	polyketide synthase multienzyme
mon AVI	polyketide synthase multienzyme
mon AVII	polyketide synthase multienzyme
mon AVIII	polyketide synthase multienzyme
mon H	regulatory protein
mon CI	flavin-dependent epoxidase
mon BII	carbon-carbon double bond isomerase
mon BI	carbon-carbon double bond isomerase
mon D	cytochrome P450 hydroxylase
mon RI	activator protein
mon AX	thioesterase

(5) a recombinant cloning or expression vector comprising a DNA sequence according to any of aspects 1-4;

(6) a transformant host cell which has been transformed to contain a DNA sequence according to any of aspects 1-4 and is capable of expressing a corresponding peptide;

(7) a hybridization probe comprising a polynucleotide which binds specifically to a region of the monensin gene cluster selected from *mon BI, mon BII, mon CI, mon CII, mon H, mon RI, mon RII, mon T, mon AIX* and *mon AX;*

(8) use of a probe according to aspect (7) in a method of detecting the presence of a gene cluster which governs the synthesis of a polyether, and optionally isolating a gene cluster detected thereby;

(9) Use of a probe comprising a polynucleotide which binds specifically to a gene responsible for levels of activity of the monensin gene cluster, preferably a regulatory gene, resistance gene or thioesterase gene, more preferably the regulatory gene *mon RI*, in a method of detecting an analogous gene in a gene cluster of another polyketide, preferably a polyether, and optionally manipulating the gene detected thereby to alter the level of expression of said other polyketide;

(10) a host cell, preferably *Streptomyces cinnamonensis*, containing a heterologous gene under the control of the *mon RI* gene and a monensin promoter;

(11) use of a portion of the monensin gene cluster having chain terminating activity, preferably comprising at least one of *mon AIX* and *mon AX* or a mutant or allele thereof having chain terminating activity, to effect chain release of a peptide other than one required for monensin biosynthesis;

(12) use of a portion of the monensin gene cluster having carbon-carbon double bond isomerase activity, preferably comprising at least one of *mon BI* and *mon BII*

or a mutant or allele thereof having isomerase activity to provide a desired stereochemical outcome in the synthesis of a polyketide other than monensin;

(13) a polypeptide encoded by a portion of the monensin gene cluster, preferably comprising at least one of *mon BI* and *mon BII* or a mutant or allele thereof, having carbon-carbon double bond isomerase activity;

(14) an epoxidase enzyme encoded by *mon CI* or a derivative or variant thereof having epoxidase activity;

(15) a cyclase enzyme encoded by *mon CII* or a derivative or variant thereof having cyclase activity.

Some embodiments of the invention will now be described by way of example with reference to the accompanying drawings in which:

Fig 1 shows the structure of monensins A and B;

Fig 2 illustrates proposed biosynthetic pathways;

Fig 3 illustrates the proposed organization of the monensin polyketide synthase (PKS) enzyme complex; and

Fig 4 illustrates the proposed organization of the monensin biosynthetic gene cluster.

The overall gene organization of the monensin biosynthetic gene cluster, as shown in Fig 4, is similar to that previously found for many macrolide biosynthetic gene clusters, which have one or more open reading frames (ORFs) encoding large multifunctional PKSs flanked by

other genes which encode functions required for the biosynthesis of the antibiotic. In the case of monensin, there is an unusually high number of distinct ORFs encoding PKS multi-enzymes (eight in total, labelled *monAI* to *monAVIII*) but there is again a separate module of enzymes for each cycle of polyketide chain extension, exactly as found for modular PKSs for macrolide biosynthesis (see Fig 3). Thus there are 12 condensations predicted to be required for the production of the carbon skeleton of monensin, and in agreement with this there are found to be 12 extension modules of PKS enzymes distributed among the 8 PKS ORFs. However, as mentioned in detail below, the other genes in the monensin cluster include genes which have not previously been found in any other gene cluster for the biosynthesis of a complex polyketide, and which are not significantly similar to any genes in published sequence databases. The cloned DNA for these genes is useful to allow the diagnosis that a polyketide biosynthetic gene cluster in any actinomycete, uncovered previously by conventional hybridization against a PKS gene probe from (say) the DEBS or some other characterised PKS gene cluster, is one that governs the synthesis of a polyether; and these genes are also valuable either singly or in combination as specific hybridization probes for the specific detection and

isolation of additional polyether biosynthetic gene clusters. Examples of these previously-unknown genes are the genes *monBI*, *monBII*, *monCI* and *monCII*. In addition the regulatory genes *monH* *monRI*, and *monRII* and the resistance gene *monT* and the thioesterase genes *monAIX* and *monAX* are all useful for the detection of analogous genes in other polyether clusters which are required for the rational manipulation of such genes in order to increase levels of the specific product.

The cloned and sequenced cluster of genes for monensin biosynthesis is useful secondly in the engineering of mutant strains of *S. cinnamonensis* and of other actinomycetes which are suitable strains for the high level production of either natural or novel recombinant polyketides. The sequence of the monensin cluster disclosed here shows the surprising fact, that the gene cluster contains a gene *monRI* whose gene product has an amino acid sequence highly similar to that of *actII*-orf4, the pathway-specific activator gene which activates the *actI* and other promoters of the actinorhodin biosynthetic gene cluster of *Streptomyces coelicolor*. The recognition of this aspect of the natural regulation of a Type I PKS cluster is important and valuable because first, it is possible to increase the yield of monensin by increasing the level of the activator MonRI, either by

placing the gene *monRI* under the control of a powerful promoter or arranging for the presence within the cells of one or more additional copies of the *monRI* gene (as exemplified below); secondly, it will be possible to use the *monRI* gene as a specific hybridisation probe to locate similar genes in other complex PKS gene clusters, especially other polyether PKS gene clusters but also polyene and macrolide gene clusters and all other Type I modular PKS gene clusters; even in cases where (as for rapamycin and erythromycin) no such gene has been previously found within the currently accepted physical limits of the relevant biosynthetic gene cluster. In such cases the *monRI* gene probe might be expected to uncover the activator even if it resides on the chromosome at some distance from the main body of the gene cluster; and simple experiments would then show whether the activator(s) so uncovered are involved in regulation of the biosynthesis of those particular metabolites; thirdly, increasing the copy number of the *monRI* gene or of any of the activator genes uncovered will tend to increase the yield of a heterologous polyketide by "crosstalk" where the activator mimics the presence of the normal activator for the transcription of the genes for that heterologous polyketide synthase. It is clear from recently published work (Wietzorrek, A. and Bibb, M. Mol. Microbiol. (1997)

25:1181-1184) that the ActII-orf4 family of activators exert their effects by binding to promoter regions within the target gene cluster, so it will be possible to use the *monRI* gene together with monensin promoter regions to drive the high-level transcription and translation of heterologous genes in *Streptomyces cinnamonensis*, and perhaps in other host strains too; such genes need not be PKS genes or even involved in polyketide biosynthesis. Monensin promoter regions are found at the 5' end of genes or groups of genes in the cluster and their location is clear from the sequence analysis disclosed here. Thus a useful vector would provide the monensin promoter and the ribosome binding site and continue up to the start of the open reading frame, after which the monensin ORF naturally found there would be replaced by the heterologous gene. The relative strength of the monensin promoters can be readily determined using any one of a number of known promoter probes, i.e. genes whose expression gives rise to readily measurable and quantifiable effects, such as Green Fluorescent Protein (GFP); or beta-galactosidase in the presence of a chromogenic substrate. It should be possible to mutate randomly the small region of the monensin promoters especially likely to interact with the MonRI activator (identified by the presence of tandem heptanucleotide repeats with a common consensus sequence

between the various monensin promoters) (Wietzorrek, A. and Bibb, M. Mol. Microbiol. (1997) 25:1181-1184), and to determine the optimal DNA sequence for the maximal activation effect using either *S. cinnamonensis* (preferably - in case there are other unknown factors that make the activation function better in this strain than in other heterologous systems), or even in another host actinomycete strain. If the natural monensin promoters were mutated to have this optimal recognition sequence, then this would further increase the production of monensin. By extension, the use of this modified monensin promoter in conjunction with the *monRI* gene in heterologous systems could form the basis of further improvements in expression of polyketide synthases or other genes, either by appropriate chromosomal alterations to introduce the altered promoter and also the *monRI* gene; or by provision of vectors containing these optimised signals linked to specific genes and housed in suitable host cells.

The sequencing of the monensin cluster has uncovered another strategy for gene regulation in such Type I clusters. The previously-sequenced genes for the rapamycin biosynthetic pathway in *Streptomyces hygroscopicus* included a gene of unknown function (*rapH*). A closely similar gene has now been found in the monensin

biosynthetic gene cluster (*monH*), and it is clear from this recurrence (and the comparison of the sequences with those of database proteins) that this gene is potentially an important DNA-binding sensor gene which acts to regulate the transcription of the cluster in concert with other regulatory signals. Simple experimentation is needed in order to define whether the gene is an activator, in which case putting in another copy or increasing its transcription will have the potential to increase polyketide biosynthesis; or alternatively the *rapH* gene product may be a negative regulator, whereupon deletion of this gene may release the biosynthetic pathway from this inhibitory effect and increase yields.

There is a continuing need to develop new methods of high-level production of bioactive metabolites and other valuable gene products in actinomycetes. *Streptomyces cinnamonensis* is a recognised and very valuable industrial strain for the production of very high levels of monensin, it is readily transformable with DNA by standard methods of conjugation or of protoplast transformation, it is a host for numerous known broad range plasmids including well-known expression plasmids of both high- and low-copy number, it also grows quickly relative to other actinomycete strains (for example about three times faster than wild type *Saccharopolyspora erythraea* the

erythromycin producer, under comparable conditions) and sporulates relatively easily. Heterologous polyketides can be expressed in *Streptomyces cinnamonensis* using for example the low-copy number plasmid pCJR24 (which has no origin of replication active in actinomycetes so is maintained by integration into the chromosome) (Rowe, C. *et al.* Gene (1998) 216:215-223) or the related plasmid pCJR29 in which the polyketide synthase gene(s) are placed under the control of the *actI* promoter which is activated by the ActII-orf4 activator; or alternatively the *monAI* promoter can be substituted together with the MonRI activator; or some other pairing of activator and cognate promoter chosen from either a Type II or a Type I polyketide synthase gene cluster. As an example, the wild type strain of *Streptomyces cinnamonensis* has been used to express the plasmid pCJR29 (Rowe, C. *et al.* Gene (1998) 216:215-223) containing as insert the three ORFs for the PKS governing the production of 6-deoxyerythronolide B, the macrolide precursor of erythromycin A in *Saccharopolyspora erythraea*, these genes being placed under the control of the pathway-specific *actI* promoter from *Streptomyces coelicolor* together with its cognate activator gene *actII*-orf4. The transformed strain when cultivated in a suitable liquid medium produced 6-deoxyerythronolide B in good yield.

It is well known to the person skilled in the art that it is possible to use standard vectors unable to replicate in actinomycetes to introduce DNA into a *Streptomyces* cell, such DNA comprising two portions of contiguous DNA which are each identical to one of two portions of the cell's chromosome that are spaced up to 100 kbp apart; and that through recombination between the incoming DNA and the chromosome occurring in both portions of DNA the net result is that the chromosomal sequence is replaced by the defective sequence originally that of the incoming DNA. Such a procedure has been applied to the monensin-producing strain of *S. cinnamonensis* as described in detail below, and a strain of *S. cinnamonensis* has been obtained that carries a specific deletion in the monensin cluster and which is unable to produce the antibiotic. The use of such a strain facilitates the production of heterologous polyketides by removal of the background of monensin production.

The multiple uses of portions of the cloned and sequenced DNA from the monensin cluster will readily occur to the person skilled in the art. A surprising feature of the PKS of the monensin cluster is an unusual mechanism of polyketide chain initiation. We have found that the monensin PKS loading module has three domains, which from the amino-terminus of the protein are: a KSq domain, an

acyltransferase domain and an ACP domain. We have uncovered this organisation in the PKS for the 14-membered macrolide oleandomycin as well as in the monensin PKS, an organisation of the loading module previously only found for the 16-membered macrolides and in which the KSq domain (which looks like a ketosynthase or condensation domain except that the active site cysteine residue is substituted by a glutamine for which the single letter notation is Q) had been previously speculated to have no function. It was realised that the acyltransferase of the loading module actually has malonyl-CoA and not acetyl-CoA as a substrate and that KSq is an active decarboxylase. It appears that a better discrimination can be achieved in the selection of the smaller acetate unit over propionate if the choice is made initially between methylmalonyl- and malonyl-CoA.

An unprecedented feature of the monensin PKS genes is that no integral chain-terminating domain is present as a C-terminal appendage of the PKS extension module that catalyzes the twelfth and final chain extension. Because the product of the monensin PKS is a carboxylic acid, it would have been firmly predicted that chain release would have been catalyzed by such a C-terminal domain containing a "thioesterase" activity. Previously sequenced PKS gene sets have been of two sorts: first, those macrolide PKSs

typified by erythromycin, spiramycin, tylosin, niddamycin which have a readily recognisable C-terminal "thioesterase" domain, which in these enzymes functions as a specific cyclase rather than releasing the polyketide product as a free carboxylic acid; secondly, those macrolide PKSs typified by rapamycin, FK506, and rifamycin, where there is an alternative and recognised mode of chain termination by transfer of the polyketide chain to an acceptor moiety, catalyzed by a specific enzyme (eg pipecolate incorporating enzyme for rapamycin (Schwecke T. *et al*. Proc. Natl. Acad. Sci. USA (1995) 92:7839-7843) and FK506 (Mothamedi H. and Shafiee A, Eur. J. Biochemistry (1998) 256:528-534); arylamine synthetase for rifamycin (August P.R. *et al*. Chemistry & Biology (1998) 5:69-79).

The monensin PKS surprisingly falls into neither category, and therefore seems to be the first example of a novel mode of chain termination. It is novel and noteworthy in this connection that the monensin PKS gene cluster contains two small genes that encode discrete, monofunctional thioesterase enzymes. Although many PKS gene clusters have been previously shown to contain one such discrete thioesterase, none have been shown to have two. The role of such thioesterases is not known, although in the case of methymycin/pikromycin PKS, which has been

reported to be responsible for the biosynthesis of both the 12-membered macrolide methymycin and the 14-membered macrolide pikromycin (Xue Y.Q. Proc. Natl. Acad. Sci. USA (1998) 95:12111-12116) the disruption of this thioesterase reportedly caused a ten-fold drop in the amount of both macrolides produced. A similar finding has been reported for the discrete thioesterase of the tylosin PKS gene cluster (Cundliffe E. *et al.* Chemistry & Biology in press). Additional copies of such thioesterases may therefore accelerate the production of specific polyketide, but this has not yet been demonstrated. However, the presence of the discrete thioesterase is not completely essential for polyketide production.

It is highly desirable to have a broadly effective method of catalysing the release of polyketide gene products from a PKS as the free acid. The well-studied integral thioesterase domain in the erythromycin PKS thioesterase has a broad specificity in cyclization to form a lactone (assuming that a hydroxy group is present in the growing polyketide chain at an appropriate position), but hydrolysis to form the free acid is very slow. The recognition of the unusual arrangement of the monensin PKS means that it is now possible to harness either the entire PKS module that catalyses the twelfth and final extension cycle in monensin biosynthesis, or the

C-terminal portion of it, and graft it onto a different polyketide synthase by genetic engineering, so as to allow the release mechanism characteristic of monensin to operate in a different context. The use of this portion only of the monensin PKS suffices to allow the novel mechanism of chain release to operate successfully. The speed of the polyketide chain hydrolysis in a given case can depend on the additional presence of one or both of the discrete thioesterase genes (*monAIX* and *monAX*) from the monensin gene cluster. The use of this novel method of chain termination represents a valuable way of generating a large number of novel engineered polyketides that are currently inaccessible, and ensuring that the products have a specified chain length.

The genes *monBI* and *monBII* appear to encode very similar enzymes with significant amino acid sequence similarity to authentic ketosteroid isomerases which are known to catalyse the migration of an activated carbon-carbon double bond. The conservation of active site residues makes it very likely that these *mon* genes govern a reaction involving activated double bonds in the biosynthetic pathway to monensin and this surprising observation can be accommodated if the initial product of the polyketide chain growth on the monensin PKS is a linear precursor in which the double bonds were initially

formed with a conventional *trans* or E (entgegen) geometry; but before the polyketide chain was extended by insertion of the next unit the *monBI* and/or the *monBII* gene product(s) catalyse the specific rearrangement of the newly-created double bond into the *cis* or Z (zusammen) geometry. This new view of the monensin biosynthetic pathway allows the deduction that the *monBI* and *monBII* genes, perhaps in combination with specific portions of the monensin modules where they normally exert their effects (namely modules 3, 5 and 7) might be used in order to achieve the extremely desirable targetted biosynthesis of novel polyketides containing double bonds with Z geometry at specified point(s) along the chain. Thus for example it should be possible to provide for the direct biosynthesis of C22-C23 *cis* or Z double bond in avermectins, thus avoiding tedious and expensive chemical conversion of an initial fermentation product into this important anthelminthic. Only limited experimentation is needed to see whether the *monBI* and/or *monBII* gene products are sufficient or whether the *mon* PKS at modules 3, 5 and 7 forms part of the specific docking site(s) for the isomerases and therefore must also be used in the creation of the hybrid PKS that will insert the *cis* or Z double bond at the desired position. The substrate specificity of the isomerases need not be limited to 2,3-

unsaturated thioesters. The purified enzymes could also be used to effect such isomerisations *in vitro*, depending on the position of the equilibrium or whether further enzymes are used to achieve the further transformation of the product as it is formed (*vide infra*).

The product of the *monCI* gene is a novel oxidative enzyme with some sequence similarity to authentic examples of such enzymes in the databases; and with a clearly definable role in the monensin biosynthetic pathway, the epoxidation of the double bonds at three separate positions in the initially-formed acyclic intermediate in monensin biosynthesis. This epoxidase could therefore be used in conjunction with *monBI/monBII* gene products to effect oxidative reactions on suitable substrates *in vitro* and *in vivo*. Similarly the *monCII* gene product is a putative cyclase that opens the epoxides and causes the formation of ether rings in monensin.

Any or all of the *monBI, monBII, monCI or monCII* genes may be introduced into a heterologous strain containing the gene cluster for another polyether, in order to divert the biosynthetic pathway and produce a polyketide of altered structure. In these experiments the analogues of these *monB* genes could either be present or (once located and characterised using the *mon* genes as probes) they may be deleted prior to the introduction of

the *monB* and *monC* genes into that strain. The converse experiment in which analogues of the *monB* and *monC* genes from other strains are introduced into *S. cinnamonensis* likewise has the potential to produce novel oxidised polyketides. Also, the *monB* and *monC* genes or their analogues may be introduced into a strain that normally produces a macrolide or a polyene or some other complex polyketide and expressed there, when they may effect the diversion of the growing polyketide chain on a heterologous modular PKS towards a new product, which may or may not have the structure of a polyether.

The availability of the monensin gene sequence allows the institution of domain swaps to alter the acyltransferase (AT) specificity of a given module, for example the ethylmalonyl-CoA specific extender found in one of the modules of the monensin PKS can be used to replace one of the other ATs to generate an ethyl side branch at that position in the chain, or the AT can be used to substitute in any other (e.g. macrolide) PKS, as described in WO 98/01571 and WO 98/01546. Similarly the alteration of the level of reduction in a module, by manipulation of the reductive enzymes, can be applied to the monensin genes and here it will produce, depending on which module is affected, either an altered monensin, or a

species which is only partly cyclised, or a polyether with an altered pattern of cyclisation, or even a linear polyketide.

In general the targetted alteration of the pattern of substitution of sidechains or reduction level along the polyketide chain produced by the monensin PKS will, like the disruption or deletion of the oxidative enzymes mentioned above, lead to non-polyether polyketide products. It should be possible, by introduction of the DEBS thioesterase at the C-terminus of one of the later modules of the monensin PKS, together with an appropriately placed hydroxy group earlier in the chain, to produce novel macrolide products from this polyether PKS system, or alternatively novel polyenes of defined chain length and chosen ring size.

Example 1

Cloning of the monensin A biosynthetic gene cluster using DNA probes derived from the erythromycin-producing polyketide synthase of *Saccharopolyspora erythraea*

A genomic library of the monensin A producing strain *Streptomyces cinnamonensis* ATCC 15413 was constructed using methods well-known in the art, namely, the production of high molecular weight genomic DNA, followed by the partial cleavage of this DNA using the frequent-cutting restriction enzyme *Sau*3A, fractionation of the fragments on a sucrose gradient and selection of fragments of average size 35-40 kbp, and the cloning of these fragments into the cosmid vector pWE15 (Evans, G.A. *et al.* Gene (1989) 79:9-20) which had been previously digested with *Bam*HI and treated with shrimp alkaline phosphatase. The library was packaged and transfected into *Escherichia coli* XL-1 Blue MR cells. The library was plated out on 2xTY agar medium (10 g tryptone, 10 g yeast extract, 5 g NaCl, 15 g bactoagar per litre containing ampicillin 50 μg/ml) for cosmid selection and the colonies were allowed to grow overnight. The library was then screened by hybridisation using as a probe DNA encoding the ketosynthase domain of module 1 of the erythromycin-producing PKS (6-deoxyerythronolide B synthase, DEBS) of *Saccharopolyspora erythraea*. The colonies giving a

positive hybridisation signal in the hybridisation were selected and the cosmid DNA from each colony was purified and mapped by restriction digestion. The presence of the target biosynthetic genes on a cosmid was verified by sequencing of the ends of the cosmid inserts using the commercially available T3 and T7 primers which hybridise specifically to the respective ends of each cosmid insert (Evans, G.A. *et al.* Gene (1989) 79:9-20).

Example 2

Sequencing of the biosynthetic gene cluster for monensin A from *Streptomyces cinnamonensis*

Three cosmids obtained by screening of the genomic library of *S. cinnamonensis* were used to obtain the entire DNA sequence of the monensin biosynthetic gene cluster. These cosmids, MO.CN02, MO.CN11 and MO.CN33 between them contain the entire DNA sequence of the cluster and the adjacent regions of the chromosome. They have been deposited in NCIMB, 23 St Machair Drive, Aberdeen AB24 3RY, UK, under the NCIMB accession numbers 40956 (MO-CN11); 40957 (MO-CN33) and 40958 (MO-CN02) respectively.

The DNA of each cosmid was separately subjected to partial digestion with *Sau*3A and fragments of approximately 1.5-2.0 kbp were separated by agarose gel electrophoresis. The fragments were then ligated into the

plasmid vector pUC18 (Messing, 1982), previously digested with *Bam*HI and treated with shrimp alkaline phosphatase. The library was transformed into *E. coli* strain XL1-Blue MR and plated on 2xTY agar medium containing ampicillin (100 µg/ml) to select for plasmid-containing cells. Plasmid DNA was purified from individual colonies and sequenced using the Sanger dye-terminator procedure on an ABI 377 automated sequencer (Sanger, F. Science (1981) 214:1205-1210). The sequence data obtained from single random subclones of a cosmid was assembled into a single continuous sequence and edited using GAP4.1 program of the STADEN gene analysis package (Staden, R. Molecular Biotechnology (1996) 5:233-241).

The sequence is set out in the appended sequence listing.

Tables I and II contain data about individual genes and gene products.

Example 3

Inactivation of the monensin A biosynthetic gene cluster

A chromosomal gene disruption experiment was used to verify the identity of the cloned polyketide synthase gene cluster. Plasmid pMOB6314 is a pUC18 sequencing subclone of the presumed monensin A biosynthetic gene cluster prepared as described in Example 1, whose inserted DNA comprises the DNA sequence from nucleotide 9763 to

nucleotide 10108 in SEQ ID 1, and which therefore contains a region of DNA wholly internal to *orfE*, a putative 3-O-methyltransferase. A *Hin*dIII fragment containing the thiostrepton resistance gene *tsr* from plasmid pIJ702 (Katz, E. *et al.* J. Gen. Microbiol. (1983) 129:2703-2714) was cloned into the *Hin*dIII site of plasmid pMOB6314 and the ligation mixture was used to transform *E. coli* cells. Transformants bearing the required plasmid pMOΔE01 were identified by isolation of plasmid DNA and analysis by restriction digestion. pMOΔE01. Plasmid pMOΔE01 was used to transform protoplasts of *Streptomyces cinnamonensis* as described by (Hopwood D.A. *et al.* (1985)). Since plasmid pMOΔE01 lacks an origin of replication that is active in *Streptomyces*, growth in the presence of thiostrepton (25 µg/ml) in the regeneration medium led to the isolation of stable integrants. Isolated putative integrants were tested for the presence of integrated pMOΔE01 sequences by Southern hybridisation. A clone of *Streptomyces cinnamonensis* identified by its restriction pattern in Southern hybridisation as bearing pMOΔE01 integrated in the region of *monE* of the monensin A biosynthetic gene cluster was designated *S. cinnamonensis* MO-DD01.

Detection of production of the monensin A related metabolites produced by *S. cinnamonensis* MO-DD01 was performed by GC-MS analysis of methanol extracts of the

entire broth harvested in 72 hours of growth of the strain. No significant amounts of monensin A-related metabolite production were detectable.

Example 4

Overproduction of erythromycin aglycone in *Streptomyces cinnamonensis*

S. cinnamonensis is a suitable system for overproduction not just of monensin A but also of other polyketide metabolites. Established techniques of genetic transformation allow fast introduction of foreign polyketide producing genes sets into this host. Fast growth of *S. cinnamonensis* in liquid culture and optimal precursor supply favour high yield of polyketide metabolites.

Construction of pIB061

S. erythraea NRRL2338 was transformed with pCJR30 (Rowe, C. J., et al. (1998) Gene 216:215-223) using a routine protoplast transformation technique as described by Hopwood et al. (1985). A stable integrant of *S. erythraea* [pCJR30] was identified and the production of 10mg/L of the triketide lactone (delta lactone of (2S,3R,4R,5R)-2,4-dimethyl-3,5-dihydroxy-heptanoic acid) in addition to erythromycins was confirmed by MS analysis.

Total DNA of *S. erythraea* [pCJR30] was purified and

approximately 200 ng was digested with *Eco*RI endonuclease. The digestion mixture was precipitated with isopropanol and the resulting DNA was treated with T4 DNA-ligase for 16 hours at 16°C. The ligation mixture was used to transform *E.coli* DH10B cells. The transformants were screened for the presence of the plasmid. A clone containing a 44.7kb plasmid was identified and confirmed by restriction analysis to contain three complete genes: *ery*AI, *ery*AII and *ery*AIII. The plasmid was named pIB061.

Transformation of *S. cinnamonensis*

Protoplasts of *S. cinnamonensis* were prepared by a modified procedure of Hopwood *et al.* (1985). Plasmid pIB061 was transformed into the protoplasts of *S. cinnamonensis* and stable thiostrepton resistant colonies were isolated. Individual colonies were checked for their plasmid content and the presence of plasmid pIB061 was confirmed by its restriction pattern. *S. cinnamonensis* (pIB061) was inoculated into 250 ml of M-C3 minimal production medium containing 10 μg/ml of thiostrepton and allowed to grow for 72 hours at 30 °C. After this time the mycelia were removed by filtering. The broth was extracted with two volumes of ethyl acetate and the combined ethyl acetate extracts were washed with an equal volume of saturated sodium chloride, dried over anhydrous sodium sulphate, and the ethyl acetate was removed under reduced

pressure to give about 200 mg of crude product. The product was analysed by LCQ and mass was confirmed to that of erythronolide B.

This example demonstrates the importance of *S. cinnamonensis* for production of high levels of foreign polyketide antibiotics. Introduction of the complete erythromycin gene cluster or other gene clusters into this system are likely to produce high levels of the corresponding metabolites.

Example 5

Construction of plasmid pCJW58 containing the monensin activator gene under the ermE* promoter

The ermE* promoter derived from the *ermE* resistance methyltransferase gene of *S. erythraea* (Bibb *et al.* Gene (1985) 38:215-226) was amplified by PCR as a *Spe*I-*Xba*I fragment using the following oligonucleotides 5'-CCACTAGTATGCATGCGAGTGTCCGTTCGAGT-3' and 5'-TTGTATACACCTAGGATGGTTGGCCGTGC-3' with pRH3 (Dhillon *et al.* Molecular Microbiology (1989) 3:1405-1414 as a template and cloned into *Sma*I-digested, phosphatase-treated pUC18, to produce plasmid pIB135. The integrative plasmid pSET152 (Bierman, M. *et al.* (1992) Gene 116:43-49)) was digested with *Xba*I and the backbone was dephosphorylated and ligated to the *Spe*I-*Xba*I fragment of pIB135 containing the *ermE** promoter. The ligation mixture was used to

transform *E. coli* DH10B and the orientation of the insert in the plasmids from individual clones was checked by using restriction analysis. A plasmid with the *ermE** promoter oriented so that the *Nde*I and *Xba*I sites are adjacent to the apramycin resistance gene was selected and named pIB139.

The *monR* gene from the monensin biosynthetic gene cluster was amplified and *Nde*I and *Xba*I restriction sites introduced at 5′ and 3′ ends respectively, by PCR using as primers the following oligonucleotides:
5′-AGA TAC CAT ATG CTG GGC CCG CTC CGC AT -3′
and 5′-AAT GCT CTA GAC TGT CAG CGA CCG GAC AGG GCC AA-3′
and cosmid MO.CN11 as template. The PCR product was ligated into *Sma*I-treated and phosphatase-treated plasmid pUC18 and the ligation mixture was used to transform *E. coli* DH10B cells. Transformant colonies were analysed for the presence of plasmid and the identity of the plasmid inserts was verified by sequencing. A plasmid whose insert contained the *monR* gene flanked by *Nde*I and *Xba*I restriction sites was selected and designated pCJW57.

Plasmid pCJW57 was digested with *Nde*I and *Xba*I and the fragment containing the monR gene was ligated together with the backbone of plasmid pIB139 which had been digested with the same two restriction enzymes, and purified by gel elution. The ligation mixture was used to

transform *E. coli* strain DH10B cells. Transformant colonies were analysed for the presence of plasmid and the identity of the plasmid inserts was verified by restriction analysis. One such recombinant was selected and named plasmid pCJW58.

Plasmid pCJW58 was used to transform the methylation-deficient *E. coli* strain ET 12567 (MacNeil D. J. et al. (1992) Gene 111:61-68) and the recovered, unmethylated plasmid was then used to transform the same *E. coli* strain ET12567 housing the plasmid pUB307, a derivative of RP4 which is *mob*⁻ and which contains a gene for kanamycin resistance (Piffaretti, J. C. et al. (1988) Mol. Gen. Genet. 212:215-218). Recombinants were plated on 2 x TY agar medium containing apramycin and kanamycin at final concentrations of 50 micrograms per ml and 50 micrograms per ml respectively. The plasmid content of recombinants was checked isolation of plasmid DNA and checking of the identity of these plasmids by restriction analysis. One such clone which contained both pUB307 and plasmid pCJW58 was selected and used for further experiments.

Construction of *Streptomyces cinnamonensis* (pCJW58) and production of monensins

A single colony of *E. coli* ET12567 housing both pUB307 and pCJW58 was toothpicked into 3 ml of TY liquid medium, containing apramycin and kanamycin at 25 and 25

micrograms respectively, and grown overnight at 37°C. This culture was used to inoculate 25 ml of TY medium, supplemented with the same antibiotics at the same concentrations, and growth was continued until the absorbance at 600 nm (1 cm pathlength) was between 0.3-0.6. The cells were centrifuged (room temperature, 7 minutes, 2000 x *g*), resuspended in TY liquid medium (10 ml) containing no added antibiotics, re-centrifuged as before, then resuspended in 2ml of TSB medium and placed on ice. Meanwhile, 0.5 ml of TSB medium was added to 100 microL containing approximately 10^8 spores of *S. cinnamonensis*. After a brief heat shock, at 50°C for 10 minutes, the suspension was briefly cooled, mixed with 0.5 ml of donor *E. coli* cells, and plated on solid A medium, which has composition as follows:

A medium

Sigma wheat starch	5g
Corn steep powder	1.25g
Yeast extract	1.5g
$CaCO_3$	1.5g
$FeSO_4$	6 mg
DIFCO agar	10g
H_2O	to 500 ml

pH adjusted to pH 7 with KOH.

And to which in addition was added 10 mM $MgCl_2$ to a final concentration of 10 mM.

The plates were allowed to dry overnight at room temperature, and were then allowed to incubate a further 18 hours at 30°C. After this time each 25 ml plate was overlaid with a solution of apramycin (final concentration 50 micrograms per ml) and nalidixic acid (final concentration 20 micrograms per ml), and the plates were allowed to incubate for four days at 30°C. At this time individual colonies were toothpicked onto solid A medium and allowed to grow. Four representative colonies from the A medium plate were grown up in liquid modified YEME medium, which has composition as follows:

Modified YEME medium

Sucrose	100g
DIFCO Yeast extract	3g
Bacto peptone	5g
Oxoid Malt extract	3g
Glucose	10g

H_2O to 1L

pH adjusted to pH 7.2 with NaOH.

These cultures were used to provide a 2% vol/vol inoculum for 30 ml of modified YEME which was grown for 7 days, and then transferred to SM16 medium, which has

composition as follows:

SM16 medium

3-[N-Morpholino]-propane sulfonic acid (MOPS) buffer	20.9g
L-proline	10.0g
Glucose	20g
NaCl	0.5g
K_2HPO_4	2.1g
Ethylenediaminetetraacetic acid, sodium salt	0.25g
$MgSO_4.7H_2O$	0.49g
$CaCl_2.2H_2O$	0.029g
Trace elements solution (Hopwood, D. A. et al. (1985) Genetic Manipulation of *Streptomyces* - a Laboratory Manual, at p.235)	2 ml
0.5 M $CoCl_2$ solution	2 microlitres
H_2O to 1L	
pH adjusted to pH 7 with NaOH.	

After growth for a further 7 days, mycelium was collected by centrifugation at 2000 x g for 30 minutes, and the supernatant was extracted three times with 300 ml of ethyl acetate. The combined extracts were concentrated by evaporation under reduced pressure to an oil, which was

mixed with 1 ml of methanol. Samples were applied to an LCQ liquid chromatograph fitted with a mass spectrometer detector unit. The column used was a C18 reversed phase column, equilibrated with a mixture of 80% 20mM ammonium acetate/20% acetonitrile, and the column was eluted with a gradient of increasing acetonitrile, reaching 100% acetonitrile over 24 minutes. Monensins A and B emerged from the column with retention times respectively of 8.2 minutes and 9.2 minutes. The relative amounts of monensin produced by three independent clones (A-C) containing an additional copy of the *monR* gene were compared to a control fermentation of the wild type *S. cinnamonensis* strain, with the results shown in the Table below:

Table showing increased monensin production in strains bearing additional copy of *monR* gene

Strain	monensin A concentration (arbitrary units)	monensin B concentration (arbitrary units)
Control	188	861
A	430	1 800
B	450	1 300
C	249	1 300

Example 6

Construction of *S. cinnamonensis* M12AT5

A region lying immediately 5′ of the DNA encoding the

acyltransferase (AT12) domain of module 12 of the monensin polyketide synthase in the monensin biosynthetic gene cluster was amplified with the following primers: 5'-GGTGGCCACGGAAACACCAACACCGGACCCGCGCC-3', and 5'-CTCTCGGAGGCCCGGCGCAACGGCCACAA-3', 3' using cosmid MO-CN11 as a template. The PCR product was ligated into *Sma*I digested and phosphatase-treated plasmid pUC18 and the ligation mixture was used to transform *E. coli* DH10B cells. Transformant colonies were analysed for the presence of plasmid and the identity of the plasmid inserts was verified by sequencing. A plasmid whose insert contained a fragment upstream of the AT12-encoding sequence from about 82.3kb to 83.2kb of the *mon* cluster was designated pMO81. Similarly a region lying immediately 3' of the DNA encoding the acyltransferase (AT12) domain of module 12 of the monensin polyketide synthase in the monensin biosynthetic gene cluster was amplified with the following primers: 5'-GGCCTAGGGCTGCCTCGGGTGGTGGATCTGCCGA-3' and 5'- TGGTCGGGCGCGGTGCGTGCGATACGT-3', using cosmid MO-CN11 as a template. The PCR product was ligated into *Sma*I-treated and dephosphorylated pUC18 and the ligation mixture was used to transform DH10B *E.coli* cells. Transformant colonies were analysed for the presence of plasmid and the identity of the plasmid inserts was verified by sequencing. A plasmid whose insert contained

a fragment downstream of the AT12-encoding sequence, from 80.5kb to 81.4kb of the *mon* cluster, was designated pMO82.

The DNA encoding AT of module 5 was amplified and *Msc*I and *Avr*II restriction enzyme recognition sites were introduced at the ends by PCR using the following primers: 5'-CCTGGCCAGGGCGGCCAGTGGGTGGGCATG-3' and 5'-GGCCTAGGGGTCGGCCGGGAACCAGCGCCGCCAGT-3' and the cosmid MO-CN33 as a template. The PCR product was ligated into *Sma*I-treated and dephosphorylated pUC18 and the ligation mixture was used to transform DH10B *E.coli* cells. Transformant colonies were analysed for the presence of plasmid and the identity of the plasmid inserts was verified by sequencing. A plasmid whose insert DNA, with sequence from about 44.2kb to 45.2kb of the *mon* cluster, encoded the AT5 domain was designated pMO83.

pMO81 was digested with *Msc*I and *Hind*III and ligated to the 0.9kb *Msc*I - *Hind*III fragment of pMO82. A clone containing both fragments was designated pMO84. Plasmid pMO84 was cleaved with *Avr*II and *Hind*III, treated with phosphatase, and ligated together with the 1.0 kb *Avr*II - *Hind*III fragment of pMO83 to produce pMO85, which contains the DNA encoding the AT5 domain flanked by DNA from either side of the DNA encoding the AT12 domain of the monensin PKS. The thiostrepton resistance gene *tsr*, derived from plasmid pIJ702 (Katz, E. et al., J. Gen. Microbiol.

1983), was cloned into the *Hin*dIII site of pMO85. The resulting plasmid pMO86 was analysed by its restriction pattern and confirmed to contain all the desired elements.

Plasmid pMO86 was used to transform *S. cinnamonensis* protoplasts as described by Hopwood, D. A. (1985). Stable thiostrepton-resistant transformants were isolated and checked for the desired integration of the pMO85 into the AT12 flanking regions by Southern blot hybridisation. One such integrant, *S. cinnamonensis* MO-08, containing pMO85 integrated upstream of the AT12, was passed through 4 cycles of sporulation on a non-selective nutrient medium. Spores obtained after the fourth cycle were replica-plated onto media with and without thiostrepton. DNA of clones that had lost thiostrepton resistance was analysed by Southern blot hybridisation. Clones in which the DNA encoding the AT12 domain had been replace by the DNA encoding the AT5 domain was designated *S. cinnamonensis* M12-AT5. At this time individual colonies were toothpicked onto solid A medium and allowed to grow. Four representative colonies from the A medium plate were grown up in liquid modified YEME medium, which has composition as follows:

Modified YEME medium

Sucrose	100g
DIFCO Yeast extract	3g
Bacto peptone	5g
Oxoid Malt extract	3g
Glucose	10g

H_2O to 1L

pH adjusted to pH 7.2 with NaOH.

These cultures were used to provide a 2% vol/vol inoculum for 30 ml of modified YEME which was grown for 7 days, and then transferred to SM16 medium, which has composition as follows:

SM16 medium

3-[N-Morpholino]-propane sulfonic acid (MOPS) buffer	20.9g
L-proline	10.0g
Glucose	20g
NaCl	0.5g
K_2HPO_4	2.1g
Ethylenediaminetetraacetic acid, sodium salt	0.25g
$MgSO_4.7H_2O$	0.49g
$CaCl_2.2H_2O$	0.029g

Trace elements solution (Hopwood, D. A. et al. (1985) Genetic

Manipulation of *Streptomyces* - a Laboratory Manual, at p.235) 2 ml

0.5 M $CoCl_2$ solution 2 microlitres

H_2O to 1L

pH adjusted to pH 7 with NaOH.

After growth for a further 7 days, mycelium was collected by centrifugation at 2000 x g for 30 minutes, and the supernatant was extracted three times with 300 ml of ethyl acetate. To confirm presence of the C-2-ethyl substituents of both monensin A and B the combined extracts were concentrated by evaporation under reduced pressure to an oil, which was mixed with 1 ml of methanol. Samples were applied to an LCQ liquid chromatograph fitted with a mass spectrometer detector unit. The column used was a C18 reversed phase column, equilibrated with a mixture of 80% 20mM ammonium acetate/20% acetonitrile, and the column was eluted with a gradient of increasing acetonitrile, reaching 100% acetonitrile over 24 minutes. Mass ions 14 mass units above those expected for both monensin A and B confirmed production of the respective C-2-ethyl substituents.

Example 7. Construction of pSGK005 and its use in the production of C-13 propyl-erythromycin

Plasmid pSGK005 is a pCJR24 based plasmid containing a PKS gene comprising a loading module plus the first and

second extension modules and the chain terminating thioesterase of the PKS responsible for the production of erythromycin (DEBS). The loading module comprises the KS and ethyl-malonyl CoA specific AT from module 5 of the monensin PKS linked to the DEBS loading ACP domain. In addition, the active site cysteine of this module 5 KS has been mutated to glutamine to convert an extender di-domain to a loading di-domain. Plasmid pSGK005 was constructed as follows.

A 2769bp DNA segment of the monensin cluster of *S. cinnamonensis* extending from nucleotide 42438 to 45207 was amplified by PCR using the following oligonucleotide primers. 5'-GTGACGTCATATGTCGAGTGCTGAAGAGTCG-3' and 5'-GGGGTCGCCTAGGAACCAGCGCCGCCAGTCGA-3'

The design of these primers introduced *Nde* I and *Avr* II sites at the ends of the amplifed fragment. Monensin cosmid 05 was used as a template for the reaction. The resulting 2769bp fragment was digested with *Nde* I and *Xho* I and a 656bp fragment (Fragment A) purified by preparative gel electrophoresis.

A second PCR reaction was used with the same template to amplify DNA from nucleotide 43098 to 45207. The primers used were 5'-CGGCCTCGAGGGCCCGTCGGTCAGTGTCGACACGGCGCAGTCCTCCTCGC-3' and 5'-GGGGTCGCCTAGGAACCAGCGCCGCCAGTCGA-3'

The design of the upstream oligonucleotide primer incorporated a change of the codon specifying the KS active site cysteine (nucleotides 43135-43137, TGC) to glutamine (CAG). The resulting 2109bp DNA fragment (Fragment B) was digested with *Xho* I and *Avr* II and purified by preparative gel electrophoresis.

Plasmid pCJW80 is derived from pCJR24 and DEBS1-TE in which *Msc* I and *Avr* II sites have been introduced to flank the AT of the DEBS loading module. This plasmid was digested with *Nde* I and *Avr* II and the larger fragment (Fragment C) purified by preparative gel electrophoresis.

The three fragments (Fragments A, B, C) were ligated together using T4 DNA ligase and the ligation mixture used to transform electrocompetent *E. coli* DH10B cells. Individual clones were checked for the presence of the desired plasmid pSGK005. The identity of pSGK005 was confirmed by restriction pattern and sequence analysis.

Plasmid pSGK005 was used to transform *S. erythraea* NRRL2338 using a routine protoplast transformation technique. Thiostrepton resistant colonies were selected on R2T20 media containing g/ml thiostrepton. Further analysis confirmed that pSGK005 had integrated into the *S. erythraea* NRRL2338 chromosome by Southern blot hybridisation of their genomic DNA with DIG-labelled DNA containing the *act*II orf4 promoter. The culture *S.*

erythraea NRRL2338 (pSGK005) was inoculated into 5ml tap water medium in a 30ml flask. After three days incubation at 29°C this flask was used to inoculate 30ml of Ery-P medium in a 300ml flask. The broth was incubated at 29°C at 200rpm for 6 days. After this time the whole broth was adjusted to pH8.5 with NaOH, and then extracted twice with an equal volume of ethyl acetate. The ethyl acetate extract was evaporated to dryness at 45°C under a nitrogen stream using a Zymark Turbovap LV evaporator. The product identities were confirmed by LC/MS. A peak was observed with a m/z value of 734 $(M+H)^+$ required for erythromycin A. A second peak was observed with a m/z value of 748 $(M+H)^+$, required for 13-propyl erythromycin A.

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TABLE I

gene	function	start	end
gdhA	glutamate dehydrogenase (partial)	1038	0
dapA	dihydrodipicolinate synthase	2140	1220
orf3	putative transcriptional activator	2211	3152
orf4	hypothetical protein	3264	3680
orf5	hypothetical protein	4307	3684
orf6	hypothetical protein	4570	4758
orf7	hypothetical protein	5058	5612
acpX	acyl carrier protein	6010	5693
ksX	ketoacyl synthase	8531	6045
monCI	probable epoxihydrolase/cyclase	9542	8643
monE	methyltransferase	10426	9596
monT	monensin resistance gene (ABC-	10656	12191
monRI	probable repressor	12205	12780
monAI	thioesterase	13829	13023
monAI	polyketide synthase loading &	14121	23198
	KS-L	14172	15486
	AT-L malonate specific	15777	16880
	ACP-L	17019	17276
	KS1	17358	18626
	AT1 methylmalonate specific	18960	19976
	DH1 (potential)	20019	20519
	KR1 (inactive)	21636	22241
	ACP1	22536	22793
monAI	polyketide synthase module 2	23205	29921
	KS2	23307	24569
	AT2 methylmalonate specific	24891	25913
	DH2	25953	26369
	ER2	27600	28463
	KR2	28485	29042
	ACP2	29313	29570
monAI	polyketide synthase modules 3 & 4	29974	42372
	KS3	30076	31347
	AT3 malonate specific	31798	32838
	DH3	32884	33465
	KR3	34692	35181
	ACP3	35553	35811
	KS4	35899	37170
	AT4 methylmalonate specific	37489	38511
	DH4	38557	38982
	ER4	40123	40986
	KR4	41005	41562
	ACP4	41848	42105
monAI	polyketide synthase modules 5 & 6	42448	54564
	KS5	42628	43890
	AT5 ethylmalonate specific	44221	45243
	DH5	45289	45744
	KR5	46785	47337
	ACP5	47593	47850

	KS6	47947	49218
	AT6 malonate specific	49579	50601
	DH6	50644	51075
	ER6	52222	53102
	KR6	53101	53661
	ACP6	54052	54306
monA	polyketide synthase modules 7 & 8	54614	66934
	KS7	54716	55978
	AT7 methylmalonate specific	56300	57319
	DH7	57358	57802
	KR7	59048	59608
	ACP7	59867	60124
	KS8	60185	61453
	AT8 malonate specific	61808	62839
	DH8	62882	63316
	ER8	64577	65437
	KR8	65456	66016
	ACP8	66404	66661
monA	polyketide synthase module 9	66952	72054
	KS9	67075	68340
	AT9 malonate specific	68698	69729
	KR9 (potential)	70735	71262
	ACP9	71536	71783
monH	probable regulator	72051	74993
monCI	FAD containing epoxidase	76541	75051
monBI	double bond isomerase	76960	76538
monBI	double bond isomerase	77450	77016
monA	polyketide synthase modules 11 &	88708	77447
	KS11	88612	87344
	AT11 methylmalonate specific	87022	85993
	KR11	85111	84562
	ACP11	84292	84035
	KS12	83962	82694
	AT12 methylmalonate specific	82354	81335
	DH12 (potential) delta	81286	80855
	ER12 (potential)	79618	78914
	KR12	78895	78337
	ACP12	78070	77812
monA	polyketide synthase module 10	93741	88816
	KS10	93636	92368
	AT10 methylmalonate specific	92040	91021
	KR10	90132	89584
	ACP10	89322	89068
monD	P450 oxygenase	94081	95273
monRI	probable activator	96141	95338
monA	thioesterase	96941	96138
orf29	cell wall biosynthesis capK	97580	98953
lipB	lipase B	99983	98991
orf31	ion pump	101433	100507
orf32	membrane structural protein	102581	101490
amtA	glycine amidinotransferase	102924	103450

TABLE II

GdhA, glutamate dehydrogenase (partial coding sequence) Length: 346 amino acids

```
  1  LTTRPDTKTA LSQKTALSQL LTEIEHRNPA QPEFHQAARE VLETLAPVIA
 51  ARPEYAEAGL IERLCEPERQ IVFRVPWQDD HGRVRVNRGF RVEFNSALGP
101  YKGGLRFHPS VNLGVIKFLG FEQIFKNALT GLGIGGGKGG SDFDPRGRSD
151  AEVMRFCQSF MTELYRHIGE HTDVPAGDIG VGGREIGYLF GQYRRITNRW
201  EAGVLTGKGR NWGGSLIRPE ATGYGNVLFA AAMLRERGET LEGRTAVVSG
251  SGNVAIYTIQ KLAALGANAV TCSDSSGYVV DEKGIDLDLL KQVKEVERAR
301  VDTYAQRRGA SARFVPGRRV WEVPADIALP SATQNELDAD DATALI
```

DapA, dihydrodopicolinate synthase Length: 307 amino acids

```
  1  MTLASSLEPT TEPLFNGLYV PLVTPFTDDL RLAPEALARL ADEALSAGAS
 51  GLVALGTTAE AATLTAEERE TVIRVCSAAC RAHGAPLIVG VGTNDTATAI
101  TALRELAARG DVAAALVPAP PYIRPGEAGT LAHFAALAEH GGLPLVVYDI
151  PYRTGQTLGA GTITALGRLP EVVGIKHATG SIDPTTMELL DSPLPGFAVL
201  GGDDIVLSPL VAAGAHGGIV ASANLRTADY AEMIALWRRG SAAPARALGA
251  DLARLSAALF TEPNPTVIKG VLHAQNRIPS PAVRMPLLAA SADSVRRAAP
301  LAASRK*
```

ORF3, putative transcriptional activator protein Length: 314 amino acids

```
  1  MLDVRRLHLL RELDRRGTIA AVAEALTFTA SAVSQQLGVL EREAGVPLLE
 51  RSGRRVVLTP AGRSLVAHAD AVLNRLEQAV AELAGARDGI GGPLRIGTFP
101  SGGHTIVPGA LAELASRHPA LEPMVREIDS ARVSDGLRAG ELDVALVHDY
151  DFVPATPDTT VDEVPLLEEP MYLVTHAADT ATDSGSGSTL AALLGPCAEV
201  PWITARDGTT GHAMAVRACQ AAGFQPRIRH QVNDFRTVLA LVAAGQGAGF
251  VPRMAAEPSP AGVVLTKLPL FRRSKVAFRA GGGAHPAIAA FVAAATTAVE
```

```
301  RMAGSRGPAG GSE*
```

ORF4, hypothetical protein Length: 139 amino acids

```
  1  MADDAYLFLL PDRHPRLGAA LAAVGALECT ETPAVHAWLQ AHEASVSSEQ
 51  VRILPADAET LIPKDAERLP VPLSEEEALK VEQECAPQTV TDMESELLAF
101  RETTQDWQAL VHRALTAGIP AQRIARLTGL DPEEIGRL*
```

ORF5, hypothetical protein Length: 208 amino acids

```
  1  LAVAACAAVV LPIDAVVRIS AADVGVLVFF AYLLPYLAIT MTVFVSVAPE
 51  QVRSWARREA RGTFLQRYVL GTAPGPGGSL FIAAAALVVA VLWLPGHLST
101  TFSALPRTLV ALALVVAAWI CVVVAFAVTF QADNLVENER ALEFPGERSP
151  AWADYVYFAL AAMTTFGTTD VDVTSRDMRR TVAANTVIAF VFNTVTVAIL
201  VSALGGR*
```

ORF6, hypothetical protein Length: 63 amino acids

```
  1  MTVMDKLKQM LKGHEDKAGQ GIDKAGDFVD GKTQGKYSGQ VDTAQDKLRD
 51  QFGSDQQEPP QR*
```

ORF7, hypothetical protein Length: 185 amino acids

```
  1  MGTAQSQEQA AAPGACAAFV RFVLCGGGVG LASSFAVVAL ASWVPWALAN
 51  ALVAVVSTVV ATELHARFTF GAGGRATWRQ HAQSAGSAAA AYAVTCVAMF
101  VLQQLVAAPG AVLEQVVYLS ASALAGVARF VVLRLVVFAR NRSLPAAAAV
151  RTARPVRRVP APVPATVAHA ASRPAGPAAL CPAA*
```

AcpX, acyl carrier protein (ACP) Length: 106 amino acids

```
  1  MTSTDHTSGQ DATELEKQLA AATPEEREKL LTDTIRTQAG TLLNTTLSDD
 51  SNFLENGLNS LTALELTKTL MTLTGMEIAM VAIVENPTPA QLAHHLGQEL
101  AHTTA*
```

KsX, ketoacyl-ACP synthase Length: 829 amino acids

```
  1  VANEEKLVEY LKWTTAELHQ AQQQLRELKA AQHEPIAVVS MACRLPGKTR
 51  TPDDLWDLVS EGRDAVTGFP DDRAWELPEE RPYAELGGFL DDAAGFDAGF
101  FDISDTEAVA TEPLQRLMLH LAWETVERGH IAPHTLRSTL TGVYVGATGH
151  DYATRLETAP DELLPYLGGG TSGSLVSGRI AYALGLEGPA ISVDTACSSS
201  LVALHLACQA LRRGECGLAL AGGGTVMSTP HTFHAFAHQK SLAQDGRCKP
251  FAAAADGMGL GEGVGLVLLE RLGDARKNGH PVLAVIRGSA VNQDGAGYGL
301  AAPNGPSQQH VIRAALADAG LTPDQIDAVE AHGTGTPIGD AIEVQALLAT
351  YGADRSPDRP LWLGSVKSNT GHTQGAAGAA ALIKMVQAFR HGTLPPTLHV
401  DRPTPLAAWK KGAVRLLTEA VDWPRREEPR RVGISAFATS GTNAHLILEE
451  PPVDEAPVPD AARDQTSPVA PELPVAWSLS ARTPEALRAQ AKALVTHLAA
501  TDPAPSPAEV AYSLAATRSP LEHRAVLTGT DHTELLAAAR ALAAGEDHPD
551  LVRSTPGAGP KKIAWHFDGR PADGVTTGAA PGAKPGATFG ATFGAAFGGA
601  EFHSAFPLFA SAFDEARALL DTHLPTPLPT PHSELARFAV HTALARLLLE
651  TGVRPHTLTG DGVGHIAAAY AAGILTLDDA CRLAAAHAAA AQAAEGEQPA
701  PPDAYEPVLK QLTFQRATLT LTSTAPADTP IASADYWHHH LTSPAPTAPP
751  TPETHTLLHL GALSPEGTQT SAVSALLTAL ARLHTTGGTV DWTPLVRRTP
801  HPRTIDLPTY SFQATRYWLH DHTAHAAV*
```

MonCII, probable epoxyhydrolase/cyclase Length: 300 amino acids

```
  1  VKNLRIPVSQ TVSLNVRYRP ADGPGAPGRP FLLLHGMLSN ARMWDEVAAR
 51  LAAAGHPAYA VDHRGHGESD TPPDGYDNAT VVTDLVAAVT ALDLSGALVA
101  GHSWGAHLAL RLAAEHPDLV AGLALIDGGW YEFDGPVMRA FWERTADVVR
151  RAQQGTTSAA DMRAYLRATH PDWSPTSIEA RLADYRVGPD GLLIPRLTST
201  QVMSIVAGLQ REAPADWYPK VTVPVRLLPL IPAIPQLSDQ VRAWVAAAEA
```

251 ALEQVSVRWY PGSDHDLHAG APDEIAADLL LLARSCEAMP GGKAGVRPA*

MonE, S-adeonosylmethionine-dependent methyltransferase Length: 277 amino acids

1 VNKTVAPEPS DIGHYYDHKV FDLMTQLGDG NLHYGYWFDG GEQQATFDEA

51 MVQMTDEMIR RLDPAPGDRV LDIGCGNGTP AMQLARARDV EVVGISVSAR

101 QVERGNRRAR EAGLADRVRF EQVDAMNLPF DDGSFDHCWA LESMLHMPDK

151 QQVLTEAHRV VKPGARMPIA DMVYLNPDPS RPRTATVSDT TIYAALTDIG

201 DYPDIFRAAG WTVLELTDIT RETAKTYDGY VEWIRAHRDE YVDIIGVEGY

251 ELFLHNQAAL GKMPELGYIF ATAQRP*

MonT, putative monensin resistance gene (ABC-transporter) Length: 512 amino acids

1 MSADLGARRW WAVGALVLAS MVVGFDVTIL SLALPAMADD LGANNVELQW

51 FVTSYTLVFA AGMIPAGMLG DRFGRKKVLL TALVIFGIAS LACAYATSSG

101 TFIGARAVLG LGAALIMPTT LSLLPVMFSD EERPKAIGAV AGAAMLAYPL

151 GPILGGYLLN HFWWGSVFLI NVPVVILAFL AVSAWLPESK AKEAKPFDIG

201 GLVFSSVGLA ALTYGVIQGG EKGWTDVTTL VPCIGGLLAL VLFVMWEKRV

251 ADPLVDLSLF RSARFTSGTM LGTVINFTMF GVLFTMPQYY QAVLGTDAMG

301 SGFRLLPMVG GLLVGVTVAN KVAKALGPKT AVGIGFALLA AALFYGATTD

351 VSSGTGLAAA WTAAYGLGLG IALPTAMDAA LGALSEDSAG VGSGVNQSIR

401 TLGGSFGAAI LGSILNSGYR GKLDLDGVPE QAHGAVKDSV FGGLAVARAI

451 KSNGLADSVR SAYVHALDVV LVVSGGLGLL GVVLAVVWLP RHVGQSTAKT

501 AESEHEAADA V*

MonRII, probable repressor protein Length: 192 amino acids

1 VPGLRERKKA RTKAAIQREA VRLFREQGYT ATTIEQIAEA AEVAPSTVFR

51 YFATKQDLVF SHDYDLPFAM MVQAQSPDLT PIQAERQAIR SMLQDISEQE

```
101  LALQRERFVL ILSEPELWGA SLGNIGQTMQ IMSEQVAKRA GRDPRDPAVR
151  AYTGAVFGVM LQVSMDWAND PDMDFATTLD EALHYLEDLR P*
```

MonAIX, thioesterase Length: 269 amino acids

```
  1  MDRGTAARAP QIGDEFGAAT GNGVWLRRYH AAAEAPVRLV CFPFAGGSAS
 51  YYFGLSGLLA PGVEVLAVQY PGRQDRHAEP CLASVAELAD GVVPHLPCDG
101  KPFALFGHSL GAIVAFEVAR RLRGPAGPGL PVHLFVSGGL ARPYRPAGRS
151  GAFGDADILA HLRAMGGTDE RFFRSPELQE LVLPALRADY RAVATYEAPG
201  PGRLDCPITA LIGDADERTS PEQAATWRER TGAAFDLRVL PGGHFYLDGC
251  QEQVAAVVTE ALTAGPGV*
```

MonAI, polyketide synthase multi-enzyme MONS1, housing loading module and extension module 1 Length: 3026 amino acids

```
  1  MAASASASPS GPSAGPDPIA VVGMACRLPG APDPDAFWRL LSEGRSAVST
 51  APPERRRADS GLHGPGGYLD RIDGFDADFF HISPREAVAM DPQQRLLLEL
101  SWEALEDAGI RPPTLARSRT GVFVGAFWDD YTDVLNLRAP GAVTRHTMTG
151  VHRSILANRI SYAYHLAGPS LTVDTAQSSS LVAVHLACES IRSGDSDIAF
201  AGGVNLICSP RTTELAAARF GGLSAAGRCH TFDARADGFV RGEGGGLVVL
251  KPLAAARRDG DTVYCVIRGS AVNSDGTTDG ITLPSGQAQQ DVVRLACRRA
301  RITPDQVQYV ELHGTGTPVG DPIEAAALGA ALGQDAARAV PLAVGSAKTN
351  VGHLEAAAGI VGLLKTALSI HHRRLAPSLN FTTPNPAIPL ADLGLTVQQD
401  LADWPRPEQP LIAGVSSFGM GGTNGHVVVA AAPDSVAVPE PVGVPERVEV
451  PEPVVVSEPV VVPTPWPVSA HSASALRAQA GRLRTHLAAH RPTPDAARVG
501  HALATTRAPL AHRAVLLGGD TAELLGSLDA LAEGAETASI VRGEAYTEGR
551  TAFLFSGQGA QRLGMGRELY AVFPVFADAL DEAFAALDVH LDRPLREIVL
601  GETDSGGNVS GENVIGEGAD HQALLDQTAY TQPALFAIET SLYRLAASFG
```

651 LKPDYVLGHS VGEIAAAHVA GVLSLPDASA LVATRGRLMQ AVRAPGAMAA

701 WQATADEAAE QLAGHERHVT VAAVNGPDSV VVSGDRATVD ELTAAWRGRG

751 RKAHHLKVSH AFHSPHMDPI LDELRAVAAG LTFHEPVIPV VSNVTGELVT

801 ATATGSGAGQ ADPEYWARHA REPVRFLSGV RGLCERGVTT FVELGPDAPL

851 SAMARDCFPA PADRSRPRPA AIATCRRGRD EVATFLRSLA QAYVRGADVD

901 FTRAYGATAT RRFPLPTYPF QRERHWPAAA GVGQQPETPE LPESSESSEQ

951 AGHEREEGAR AWGGPEGRLA GLSVNDQERV LLGLVTKHVA VVLGDASGTV

1001 QAARTFKQLG FDSMAAAELS ERLGTETGLP LPATLTFDYP TPLAVAAHLR

1051 AELTGTPAPA GSAPATGALG AGDLGTDEDP VAIVAMSCRY PGGAGTPEDL

1101 WRLVADGADA IGDFPTDRGW DLARLFHPDP DRSGTSCTRQ GGFLYDAADF

1151 DAEFFDISPR EALAVDPQQR LLLECAWEAF ERAGLDPRAL KGSPTGVFVG

1201 MTGQDYGPRL HEPSQATDGY LLTGSTPSVA SGRLSFSFGL EGPALTVDTA

1251 CSSSLVTLHL AAQALRRGEC DLALAGGATV LATPGMFTEF SRQRGLAPDG

1301 RCKPFAAGAD GTGWAEGVGL VLLERLSEAR RKGHAVLAVI RGSAINQDGA

1351 SNGLTAPNGP SQQRVIRAAL AAARLTADEV DVVEAHGTGT TLGDPIEAQA

1401 LLATYGQGRS AERPLWLGSV KSNIGHTQAA AGVAGVIKMV MAMRHDLLPA

1451 TLHVDEPSGH VDWSTGAVRL LTEPVVWPRG ERPRRAAVSS FGISGTNAHL

1501 VLEEAGQDEY VAGAADDAGP VDGAVLPWVV SGRTGAALRE QARRLRELVT

1551 GGSADVSVSG VGRSLVTTRA VFEHRAVVVG RDRDTLIGGL EALAAGDASP

1601 DVVCGVAGDV GPGPVLVFPG QGSQWVGMGA QLLGESAVFA ARIDACEQAL

1651 SPYVDWSLTE VLRGDGRELS RVDVVQPVLW AVMVSLAAVW ADHGVTPAAV

1701 VGHSQGEIAA VVVAGALTLE DGAKIVALRS RALRQLSGGG AMASLGVGQE

1751 QAAELVEGHP GVGIAAVNGP SSTVISGPPE QVAAVVADAE ARELRGRVID

1801 VDYASHSPQV DAITDELTHT LSGVRPTTAP VAFYSAVTGT RIDTAGLDTD

1851 YWVTNLRRPV RFADAVTALL ADGHRVFIEA SSHPVLTLGL QETFEEAGVD
1901 AVTVPTLRRE DGGRARLARS LAQAFGAGCA VRWENWFPAT GTSTVELPTY
1951 AFQRRRYWLE APTGTQDAAG LGLAAAGHPL LGAATEIADG DIRLLTGRIS
2001 RHSHPWLAQH TLFGAAVVPA SVLAEWALRA ADEAGCPRVD DLTLRTPLVL
2051 PETAGVQVQI VVGPADARDG HRDFHVYARP DGKDASEGEG IAEGEGASEG
2101 EGASGGTDAP WTCHADGRLV AEPTGTASED SPDTVWPPPG AEPVDLGDFY
2151 ERAAATGVGY GPVFTGLRAL WRRDGELFAE AVLPQEAPET AGFGMHPALL
2201 DAALHPALLG ERPAEEDKVW LPFTLTGVTL WATGATSVRV RLTPLDDDPD
2251 ASADGRAWRV GVSDPTGAEV LTCEALVAVA AGRRELRAAG ERVSDLYAVE
2301 WVPVPGPGPV GEGADFSGWA GLGECGERWE CVGRVERWYE DLDALGAAVE
2351 GGASVPSVVL ATAAAAPGGA GDGAADALSA VRWTGALLDQ WLADARFADA
2401 RLVVITSGAV ATGDDFLPDP AAAAVRGLVE QAQVRHPGRI LLVDTEAGAG
2451 LGVGAGVDDA LLEQAVAMAL GADEPQLALR AGRVLAPRLT APQDAAVTEA
2501 ARPLDPDGTV LITGPAGAPV ADLAEHLVRT GQCRHLLLLP GDGELEEMAE
2551 ELRGLGATVD LSTADPADPT ALAEVVAAVE GDHPLTGVIH ATGVVDAFDP
2601 GDSASDLMID SASDSFAEAW SSRAGVTAAL HTATAHLPLD LFAVLSPAGA
2651 DLGIARSAAA AGADAFSAAL ALRRHTTVTT DTTAPPRTTA PPRTTASPRT
2701 TALSSSRTTG VALAYGPPTA PRPGIKGTAP GRIPVLLDAA RAHGGGSPLL
2751 GARLAARALA AESAAEGVAG LPAPLRALAV AAAAAGAPTR RTAADRKPPA
2801 DWPARLAPLS APEQLRLLID AVRTHAAAVL GRTDPEALRG DATFKQLGLD
2851 SLTAVELRNR LVEDTGLRLP TALVFRYPTP AAIAAHLRER LTSPSETTAT
2901 QRSGGQTPAA GQASSALAPG GSAAGPPAAD TVLSDLTRME NTLSVLAAQL
2951 PHTETGEITT RLEALLTRWK TTNATANDSG DGNGGDDDAA ERLKAASADQ
3001 IFDFIDNELG VGHGTSRVTP TPKAG*

MonAII, polyketide synthase multi-enzyme MONS2, housing extension module 2 Length: 2239 amino acids

```
   1  MASEEQLVEY LRRVTTELHD TRRRLVQEED RRQEPVALVG MACRFPGGVA
  51  SPEDLWDLVA AGKDAIEDFP TDRGWDLEAL YDPDPAAYGT SYVRHGGFVD
 101  DAGSFDADFF GISPREALAM DPQQRLMLET SWELFERAGI EPVSLKGSRT
 151  GVYAGVSSED YMSQLPRIPE GFEGHATTGS LTSVISGRVA YNYGLEGPAV
 201  TVDTACSASL VAIHLASQAL RQRECDLALA GGVLVLSSPL MFTEFCRQRG
 251  LAPDGRCKPF AAAADGTGFS EGIGLLLLER LSDARRNGHK VLAVIRGSAV
 301  NQDGASNGLT APNDAAQEQV IRAALDNARL TPSEVDAVEA HGTGTKLGDP
 351  IEAGALLATY GQHRARPLLL GSLKSNIGHT HATAGVAGVI KTVMAIRNGL
 401  LPATLHVEEL SPHVDWDAGA VEVVTEPTPW PETGHPRRAG VSAFGISGTN
 451  AHLILEEAPP EEDVPAPVVV ESGGVVPWVV SGRTPEALRE QARRLGEFVA
 501  GDTDALPNEV GWSLATTRSV FEHRAVVVGR DRDALTAGLG ALAAGEASAG
 551  VVAGVAGDVG PGPVLVFPGQ GAQWVGMGAQ LLDESAVFAA RIAECERALS
 601  AHVDWSLSAV LRGDGSELSR VEVVQPVLWA VMVSLAAVWA DYGVTPAAVI
 651  GHSQGEMAAA CVAGALSLED AARIVAVRSD ALRQLQGHGD MASLSTGAEQ
 701  AAELIGDRPG VVVAAVNGPS STVISGPPEH VAAVVADAEA RGLRARVIDV
 751  GYASHGPQID QLHDLLTERL ADIRPTNTDV AFYSTVTAER LTDTTALDTD
 801  YWVTNLRQPV RFADTIEALL ADGYRLFIEA SAHPVLGLGM EETIEQADMP
 851  ATVVPTLRRD HGDTTQLTRA AAHAFTAGAD VDWRRWFPAD PAPRTIDLPT
 901  YAFQRRRYWL ADTVKRDSGW DPAGSGHAQL PTAVALADGG VVLNGRVSAE
 951  RGGWLGGHVV AGTVLVPGAA LVEWVLRAGD EAGCPSLEEL TLQAPLVLPE
1001  SGGLQVQVVV GAADEQGGRR DVHVYSRSEQ DASAVWQCHA VGELGRASVA
1051  RPVRQAGQWP PAGAEPVEVG GFYEGVAAAG YEYGPAFRGL RAMWRHGDDL
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1101 LAEVELPEEA GSPAGFGIHP ALLDAALHPL LAQRSRDGAG AGAHGGQVLL

1151 PFSWSGVSLW ASEATTVRVR LTGLGGGDDE TVSLTVTDPA GGPVVDVAEL

1201 RLRSTSARQV RGSAGPGADG LYELRWTPLP EPLPVPAPAN GRDVAADLSG

1251 CAVLGELVAE PGPGIDLEGC PCYPGVGALA DNASPPSMIL APVHSDTTGG

1301 DGLALTERVL RVIQDFLAAP SLEQKQTRLA FVTRGAADTG STTGGSAAPA

1351 EAVDPAVAAV WGLVRSAQSE NPGRFVLLDT DAPLDQASVA PLVDAVRSAV

1401 EADEPQVALR GGRLLVPRWA RAGEPVELAG PAGARAWRLV GGDSGTLEAV

1451 VAEACDDIVL RPLAPGQVRV AVHTAGVNFR DVLIALGMYP DPDALPGTEA

1501 AGVVTEVGPG VTRLSVGDRV MGMMDGAFGP WAVADARMLA PVPPGWGTRQ

1551 AAAAPAAFLT AWYGLVELAG LKAGERVLIH AATGGVGMAA VQIARHVGAE

1601 VFATASPGKH AVLEEMGIDA AHRASSRDLA FEDAFRQATD GRGVDVVLNS

1651 LTGELLDASL RLLGDGGRFV EMGKSDPRDP ELVALEHPGV SYEAFDLVAD

1701 AGPERLGLML DRLGELFAGG SLVPLPVTAW PLGRAREALR HMSQARHTGK

1751 LVLDVPAPLD PDGTVLVTGG TGTIGAAVAE HLARTGESKH LLIVSRSGPA

1801 AHGAEELVSR IAEFGAEATF VAADVSEPDA VAALIEGIDP AHPLTGVVHA

1851 AGVLDNALIG SQTTESLTRV WAAKAAAAQQ LHEATRESRL GLFVMFSSFA

1901 STMGTPGQAN YSAANAYCDA LAALRRAEGL AGLSVAWGLW EATSGLTGTL

1951 SAADRARIDR YGIRPTSAAR GCALLAAARA HGRPDLLAMD LDARVPAASD

2001 APVPAVLRTL AAAGAPATAR PTAAAAADGA TDWSGRLAGL TEEARLELLT

2051 ELVCTHAAGV LGHADAGAVQ VDAPFKELGF DSLTAVELRN RIAAATGLKL

2101 PAALVFDYPQ ARVLAAHLAE RLVPEGAGAM GGVSGAEGVR DAYGAGGPGG

2151 DMTAQVLLEV ARVEHTLSAA VPHGLDRAAV AARLEALLAR CTATTAATGA

2201 AGAAVEGDGD SDGDGAVDQL ETATAEQVLD FIDNELGV*

MonAIII, polyketide synthase multi-enzyme MONS3, housing extension modules 3 and 4 Length: 4133 amino acids

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   1  MVSEEKLVDY LKRVSADLHA TRQRLREAEE RGQEPVAVVE AACRYPGGIR
  51  TPEDLWDLVA AGGNALGAFP DNRGWDLRRL FHPDPDHPGT TYAREGGFLH
 101  DADLFDPEFF GISPREAAVL DPQQRLLLEC AWEALERAGI DPRSLQGSRT
 151  GVYAGAALPG FGTPHIDPAA EGHLVTGSAP SVLSGRLAYT FGLEGPAVTI
 201  DTACSSSLVA VHLAAHALRQ RECDLALAGG VTVMTTPYVF TEFSRQRGLA
 251  ADGRCKPFAA AADGTAFSEG AGLLVLERLS DARRAGHRVL AVIRGSAVNQ
 301  DGASNGLTAP NGPAQQRVIR AALAGARLSP AEVDAVEAHG TGTRLGDPIE
 351  ADALLATYGQ ERHGGRPLWL GSVKSNIGHT QGAAGAAGLI KMVQALRHET
 401  LPATLYADEP TPHADWESGA VRLLSAPVAW PRGEHGEHTR RAGISSFGIS
 451  GTNAHLILEE APAADAEGAG GDGDGDGGGV RPVVRVGATG PREEQGQGQG
 501  QEQHQQQRQQ RQRSSMMPTP HLPWLLSARS PAALRAQADA LANHVAHADH
 551  SIADIGGTLL RRTLFEHRAV VLGTDRDERA AALAALAAGR AHPALTRAAG
 601  PARNGGTAFL FTGQGSQRPG MGRQLYDTFD VFAESLDETC ARLDPLLEQP
 651  LKPVLFAPAD TAQAAVLHGT GMTQAALFAL EVALYRQVTS FGIAPSHLTG
 701  HSVGEIAAAH VAGVFSLADA CTLVAARGRL MQALPAGGAM LAVQAAEDDV
 751  LPLLAGQEER LSLAAVNGPT AVVVSGEAAA VGEVEKALRG RGLKTKRLNV
 801  SHAFHSPLIE PMLDDFREVA RGLTFHAPTL PVVSNLTGRL ADAELMADAE
 851  YWVRHVRRPV RFHDGLRALS EQGVVRYLEL GPDPVLATMV QDGLPAPAEG
 901  EEPEPVVAAA LRSKHDEGRT LLGAVAALHT DGQPADLTAL FPADAGQVPL
 951  PTYRFQRRRY WRVAPDAAAP ARAAGLQETG HPLLPAVIRQ ADGGILLAGR
1001   LSLRTHPWLA DHTIAGGVPL PATAFVELAL LAGRHAACDT IDDLTLETPL
1051   LLDDTGTGVG AAVGAGADAL VDAIEVQLAL GAPDGSGRRA LTVHSRPADD
1101   AADDGDAADA ADAAGRGGPG GSGDLGDPGD PGDLGDGGGS RGWRRHATGI
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1151 LSAGPAAEPA APDAAPWPPA DATALDVDAL YARLDAQGYS YGPAFRAVHA
1201 AWRHGDDLYA DVRLADEQRA EADAFALHPA LLDAALHAVD ELYRGSEGRG
1251 QEQGQGGQEP EQGRGDADAP VRLPFSFSDI RHHATGATRL WVRLSPQGDD
1301 RLRLSLTDGE GGQVATVDAL QLRLIPADRW RAARPTTAAP LYHLDWHELP
1351 LPEPAETDPA AHSWAVLGAH DAGLAPAAHY PDLAALKAAV EAGEPVPDIV
1401 FAPFPAQGTE TDVPAQVRAH ARHALELLRD WLTTEAFAAA RLVVLTTGAV
1451 TARPEDGPAD LATAPVWGLV RAAQAEQPDH VVLVDIDKDI DKDTDEETDQ
1501 ATDAGTASRH ALPAALAAAA AQAETQLALR AGTVLVPRLA VVPPRTDTPA
1551 LHATAPESTT DTVDSTGIAG AAESGGTVLI TGGTGGLGQA VARHLAAAHG
1601 ARHLLLVSRR GDAAEGVAEL RADLADDGVD VRVAACDITD RDALAGLLAD
1651 IPAAHPLTAV VHTAGVIDDS LITAMTPERL DAVLAPKADA AWHLHELTRD
1701 KDLSAFVLFS SGASVLGNGG QANYAAANTF LNTLAEHRRA AGLAATSVAW
1751 GLWESASGGM AARLGDADRA RIHRTGVTGL TDEQALALFD AALTAEHPTV
1801 LATRFDRAVL RGQAAAARTLQ PALRGLVRTP RPTASAGAIG STAATGSATD
1851 ENAPSSWAAR LARLSAADRD RALNELIREQ IATVLAHPSP DTIELGRAFQ
1901 ELGFDSLTAL ELRNRLSTAT GIRLPATLVF DHPSPTALVR HLHSHLPDEA
1951 QHTSPTAPGA SAEGTAATAT GIDDDPIAIV GMACRYPGGV TSPEQLWQLV
2001 ATGTDAIGPF PEDRGWDTAG LFDPDPDQVG HSYTREGGFL YDAARFDAGF
2051 FGISPREAAA TDPQQRLLLE TAWQAFEHAG IDPAALRGTP CGVITGIMYD
2101 DYGSRFLARK PDGFEGRIMT GSTPSVASGR VAYTFGLEGP AITVDTACSS
2151 SLVAMHLAAQ ALRQGECELA LAGGVTVMAT PNTFVEFSRQ RGLAPDGRCK
2201 PFAAAADGTG WGEGAGLVVL ERLSDARRKG HRVLALLRGS AVNQDGASNG
2251 MTAPNGPSQE RVIRTALAGA GRGPEDIDVV EAHGTGTTLG DPIEAQALLA
2301 TYGQGRPEDR PLWLGSVKSN IGHTQAAAGV AGVIKMVMAL RHEQLPTTLH

2351 ADEPTPHVQW DGGGVRLLTE PVPWSRGERT RRAGVSSFGI SGTNAHLILE

2401 EPPEEDLPEP VAAEPGGVVP WVVSGRTPDA LREQARRLGE FVVGAGDVSA

2451 AEVGWSLATT RSVFEHRAVV AGRDRDDLVA GMQALAAGET PTDVVSGAAA

2501 SSGAGPVLVF PGQGSQWVGM GAQLLDESPV FAARIAECEQ ALSAYVDWSL

2551 SDVLRGDGSE LSRVEVVQPV LWAVMVSLAA VWADYGVTPA AVVGHSQGEM

2601 AAACVAGALS LEDAARIVAV RSDALRQLQG HGDMASLGTG AEQAAELIGD

2651 RPGVVVAAVN GPSSTVISGP PEHVAAVVAE AEARGLRARV IDVGYASHGP

2701 QIDQLHDLLT EGLADIRPAN TDVAFYSTVT AERLTDTTAL DTDYWVTNLR

2751 QPVRFADTIE ALLADGYRLF IEASAHPVLG LGMEETIEQA DIPATVVPTL

2801 RRDHGDTTQL TRAAAHAFTA GADVDWRRWF PADPTPRTVD LPTYAFQHQH

2851 YWLEEPSGLT GDAADLGMVA AGHPLLGACV ELAESDSYLF TGRLSRRAPS

2901 WLAEHVVAGT VLVPGAALVE WVLRAGDEAG CPTIEELTLQ APLVLPESGG

2951 LQVQVVVGAT DEQSGRRDVH VYSRSEQDAS AVWVCHAVGV VSSEMPEAAA

3001 ELSGQWPPAG AEAVDVEDFY ARAAEAGYAY GPAFQGLRAL WRHGTELFAE

3051 VVLPEQAGGH DGFGIHPALL DAALHPLMLL DRPADGQMWL PFAWSGVSLN

3101 ADRATHVRVR LSPRGEAAER DLRVVIADAT GAPVLTVDAL TLRAADPGRL

3151 GAAARGGVDG LYTVDWTPLP LPQPLPLPRT DAGGSADWVI LSDNSSAALA

3201 DAVSSATAAG GGAPWALLAP VGGGSADDGL PVVRRTLSLV QEFLAAPELT

3251 ESRLVIVTRG AVATDADGDV AASAAAVWGL IRSAQSENPG RFVLLDVEEE

3301 HLHPDGGELP YAALRHAVEE LDEPQLALRS GKFLVPRMTP AAAPEELVPP

3351 VGTSGWRLGT SGTATLENLS VIDAPEAFAP LEPGQVRISV RAAGMNFRDV

3401 LIALGMYPDK GTFAGSEGAG HVTEVGPGVT HLSVGDRVMG LFEGAFAPLA

3451 VADARMVVPI PEGWSFQEAA AVPVVFLTAW YGLVDLGRLR AGESLLIHAG

3501 TGGVGMAATQ IARHLGAEVF ATASPAKHGV LDGMGIDAAH RASSRDLDFE

3551 ETLRAATGGR GMDVVLNSLA GEFTDASLRL LAEGGRMVDM GKTDKRDPDR
3601 VAAEHAGAWY RAFDLVPHAG PDRIGEMLAE LGELFASGAL APLPVQTWPL
3651 GRAREAFRFM SQAKHTGKLV LEIPPALDPD GTVLITGGTG VLAAAVAEHL
3701 VREWGVRHLL LAGRRGSEAP GSSELAEELT ELGAEVTFAA ADVSDPDAVA
3751 ELVGKTDPAH PLTGVIHAAG VLDDAVVTAQ TPESLARVWA AKATAAHLLH
3801 EATREARLGL FLVFSSAAAT LGSPGQANYA AANAYCDALV RQRRAEGLAG
3851 LSIGWGLWQT ASGMTGHLGE TDLARMKRTG FTPLTTEGGL ALLDAARAHG
3901 RPHVVAVDLD ARAVAAQPAP SRPALLRALA AGATPGARTA RRTAAAGSVA
3951 PAGGLADRLA GLPHPERRRL LLDLVRGNVA GVLGHSDHDA VRPDTSFKEL
4001 GFDSLTAVEL RNRLAAATGL KLPAALVFDY PESATLVDHL LERLSPDGAP
4051 PPVKDAADPV LNDLGRIESS LDALALDADA RSRVTRRLNT LLSKLNGAAT
4101 AGSPADVTDL DALDALDDVS DDEMFEFIDR EL*

MonAIV, polyketide synthase multi-enzyme MONS4, housing extension modules 5 and 6 Length: 4039 amino acids

1 MSSAEESSPD VSGTGVSGTG ESATGTSSTE AKLRQYLKRV TVDLGQARRR
51 LREVEERAQE PIAIVSMACR FPGDTRTPEA LWDLVAEGGD AIDDFPTNRG
101 WDLESLYHPD PDHPGTSYVR RGGFLYDAPA FDASFFGISP REALAMDPQQ
151 RVLMETAWQL LERAGIDPAS LKLSATGVYI GAGVLGFGGA QPDKTVEGHL
201 LTGSALSVLS GRISFTLGLE GPSVSVDTAC SSSLVSMHLA AQALRQGECD
251 LALAGGVTVM STPGAFTEFS RQGALSPDGR SKAFAASADG TGFSEGAGLL
301 LLERLSDARR NGHKVLAVIR GSAVNQDGAS NGLTAPNGPS QERVIRAALA
351 NAGLGAAEVD AVEAHGTGTK LGDPIEAGAL LATYGRDRDE DRPLWLGSVK
401 SNIGHPQGAA GVAGVIKMVM ALQRELLPAT LYVDEPTPHV DWSSGSVRLL
451 TEPVPWTRGE RPRRAGVSAF GMSGTNAHVI LEEAPPEEAA AAETPAEGTG
501 AVVPWVVSGR GEEALRAQAA QLAEHVRDDD QRPASPLEVG WSLATTRSVF

551 ENRAVVVGDD RDALLDGLRS LAAGEASPDV VSGAVGPTGP GPVMVFPGQG
601 GQWVGMGARL LDESPVFAAR IAECEQALSA YVDWSLTDVL RGDGSELARI
651 DVVQPVLWAV MVALAAVWAD QGIEPAAVVG HSQGEIAAAC VVGAISLDEA
701 ARIVAVRSVL LRQLSGRGGM ASLGMGQEQA ADLIDGHPGV VVAAVNGPSS
751 TVISGPPEGI AAVVADAQER GLRARAVASD VAGHGPQLDA ILDQLTEGLA
801 GIRPAATDVA FYSTVTAGHL TDTTELDTAY WVRNVRRTVR FADTIDALLA
851 DGYRLFIEVS PHPVLNLALE GLIERAAVPA TVVPTLRRDH GDTTQLARAA
901 AHAFAAGADV DWRRWFPADP APRTVDLPTY AFQRQDFWPA PAGGRSGDPA
951 GLGLAASGHP LLGASVGLAS GDVHLLSGRV SRQSAAWLDD HVVAGQALVP
1001 GAAQVEWVLR AGDDAGCSAL EELTLQTPLV LPDTGGLRIQ VVVEAADAHG
1051 RRDVRLFSRP DDDDAFASTH PWTCHATGVL APAPTDGTNG TRDAADTLDG
1101 AWPPADAEPV PADDLYAQAD RTGYGYGPAF RGVRALWRHG KDVLAEVTLP
1151 KEAGDPDGFG IHPALLDAVL QPAALLLPPT DAEQVWLPFA WNDVALHAVR
1201 ATTVRVRLTP LGERIDQGLR ITVADAVGAP VLTVRDLRSR PTDTGRLAAA
1251 ATRDRHGLFD LEWIAPENAA ENAAGPARDA SEGWVTLGED AASLADLLAS
1301 VEAGAPAPQL VAAPVEPDRT DDGLALATHV LDLVQTWLAS PLHDSRLVLV
1351 TRGAVTDADV DVAAAAVWGL VRSAQSEHPG RFTLIDLGPD DTLAAAMQAA
1401 HLEEPQLAVH GGEIRVPRLV RATTDPTAPN GTPEADRTAD PSEGLHRNGT
1451 VLITGGTGVL GRLVAEHLVT EWGVRHLLLA SRRGDQAPGS AELRARLSEL
1501 GASVEIAPAD VGDAEAVAAL IASVDPAHPL TGVIHAAGVL DDAVITAQTP
1551 ESLARVWATK ATAARHLHEA TRETPLDFFV VFSSAAASLG SPGQANYAAA
1601 NAYCDALVQH RRAQGLAGLS IAWGLWQATS GMTGQLSETD LARMKRTGFA
1651 ALTDEGGLAL LDAARAHDRA YVVAADLDPR AVTDGLSPLL RALTAPATRR
1701 RVASEGLADG ALATRLAGLD ADGRLRLLTD VVREYVAAVL GHGSAARVGV

1751 DIAFKDLGFD SLTAVELRNR LSAACDVRLP ATLIFDHPTP QALATHLVDR

1801 LAGSTSATTT VNATAPAAAH VAAGADVDAD TDDPVAIVAM TCRFPGGVAS

1851 PDDLWDLLDA RKDAMGAFPT DRGWDLERLF HPDPDHPGTS YTDQGGFLPD

1901 AGDFDAAFFG INPREALAMD PQQRLLLEAS WEVLERAGID PTTLKGTPTG

1951 TYVGLMYHDY AKSFPTADAQ LEGYSYLAST GSMVSGRVAY TLGLEGPAVT

2001 VDTACSSSLV SIHLATQALR HGECDLALAG GVTVMADPDM FAGFSRQRGL

2051 SPDGRCKAYA AAADGVGFSE GVGVLLLERL SDARRHGRRV LGVVRGSAVN

2101 QDGASNGLTA PNGPSQERVI RQALASGGLS SVDVDVVEGH GTGTTLGDPI

2151 EAQALLATYG QGRPEDRPLW LGSVKSNIGH TQAAAGVAGV IKMVMAMRHG

2201 VVPASLHVDV PSPHVEWDSG AVRLAVESVP WPQVEGRPRR AGVSSFGASG

2251 TNAHVIVESV PDGLEEDSVS VGGEALETET DGRLVPWVVS ARSPQALRDQ

2301 ALRLRDFASD ASFRAPLADV GWSLLKTRAL HEHRAVVVGA ERAELIAALE

2351 ALATGEPHAA LVGPACSQAR VGGDDVVWLF SGQGSQLVGM GAGLYERFPV

2401 FAAAFDEVCG LLEGPLGVEA GGLREVVFRG PRERLDHTVW AQAGLFALQV

2451 GLARLWESVG VRPDVVLGHS IGEIAAAHVA GVFDLADACR VVGARARLMG

2501 GLPEGGAMCA VQATPAELAA DVDGSAVSVA AVNTPDSTVI SGPSDEVDRI

2551 AGVWRERGRK TKALSVSHAF HSALMEPMLA EFTEAIRGVK FRQPSIPLMS

2601 NVSGERAGEE ITDPEYWARH VRNAVLFQPA IAQVADSAGV FVELGPAPVL

2651 TTAAQHTLDE SDSQESVLVA SLAGERPEES AFVEAMARLH TAGVAVDWSV

2701 LFAGDRVPGL VELPTYAFQR ERFWLSGRSG GGDAATLGLV AAGHPLLGAA

2751 VEFADRGGCL LTGRLSRSGV SWLADHVVAG AVLVPGAALV EWALRAGDEV

2801 GCVTVEELML QAPLVVPEAS GLRVQVVVEE AGEDGRRGVQ IYSRPDADAV

2851 GGDDSWICHA TGVLSPESAR LDTELGGVWP PAGAEPLDVD GFYAQAGEAG

2901 YGYGPAFRGL RAVWRHGQDL LAEVVLPEAA GAHDGYGIHP ALLDATLHPL

2951 LAARFMDGSE DDQLYVPFGW AGVSLRAVGA TTVRVRLRPV GESVDQGLSV

3001 TVTDATGGPV LSVDSLQTRP VKPSQLAAAQ QPDVRGLFTV EWTPLPQTDA

3051 DGEADWVVLS DGVGRLADVV SAAGGEAPWA VVAPVDASVG DGREGLDGRL

3101 VVERVLSLVQ EFLALPELAE SRLLVVTRGA VATGVDGDGD VDASAAAVWG

3151 LVRSAQSENP GRFILLDVDG DGDDQGPDLN GRHLPHATLR HAAEELDEPQ

3201 LALREGTLYV PRLTQARQSA ELVVPPGEPA WRLRMVHDGS LDALAAVACP

3251 EALEPLAPGQ VRIAVHAAGI NFRDVLVALG MVPAYGAMGG EGAGVVTEVG

3301 PEVTHVSVGD RVMGVFEGAF GPVVIAEARM VTPVPQGWDM REAAGIPAAF

3351 LTAWYGLVEL AGLKAGERVL VHAATGGVGM AAVQIARHVG AEVFATASPG

3401 KHAVLEEMGI DAAHRASSRD LAFEGTFREA TGGRGMDVVL NSLAGEFIDA

3451 SLRLLGDGGR FLEMGKTDVR AAEEVAAEHA DVSYTAYDLV GDAGPDRISN

3501 MLDKLVELFA SERLKPLPVR SWPLDKAQEA FRFMSQAKHT GKLVLEIPPA

3551 LDPEGTVLVT GGTGALGQVV AEHLVREWGV RHLLLASRRG PEAPGSDELA

3601 SKLTGLGAEV TIVAADVSDP ASVVELVGKT DPSHPLTGVV HAAGVLEDGV

3651 VTAQTPEGLA RVWAAKAAAA ANLHEATREM RLGLFVVFSS AAATLGSPGQ

3701 ANYAAANAYC DALMQHRRAV GQVGLSVGWG LWEAPDAKPG VAADAKASAA

3751 TVGKASALSD GTNGSAPQDT TGTAPQGMTG GLTDTDVARM ARIGVKGMSN

3801 AHGLALFDAA HRHGRPHLVG FNLDLRTLAT HPLHTRPALL RGLATPTAGG

3851 ASRPTATAGG QPADLAGRLA ALSPSDRHHT LVRLIREQAA TVLGHHPDSL

3901 TTGSTFKELG FDSLTAVELR NRLSAATGLR LPAGLVFDHP DADILAEHLG

3951 AQLAPDGDTP AGAEATDPVL RDLAKLENAL SSTLVEHLDA DAVTARLEAL

4001 LSNWKAASAA PGSGSTKEQL QVATTDQVLD FIDKELGV*

MonAV, polyketide synthase multi-enzyme MONS5, housing extension modules 7 and 8 Length: 4107 amino acids

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   1  MASEEELVDY LKRVAAELHD TRQRLREVED RRQEPVAVVG MACRFPGGIE
  51  TPEGLWELVA AGDDAIEPFP TDRGWDLEGI YHPDPDHPGT CYVREGGFLA
 101  APDRFDSDFF GFSPREALAS SPQLRLLLET SWEALERAGI NPASLKGSPT
 151  GVYVGAATTG NQTQGDPGGK ATEGYAGTAP SVLSGRLSFT LGLEGPAVTV
 201  ETACSSSLVA MHLAANALRQ GECDLALAGG VTVMSTPEVF TGFSRQRGLA
 251  PDGRCKPFAA AADGTGWGEG AGLILLERLS DARRKGHKVL AVIRGSAINQ
 301  DGASNGFTAP NGPSQRRVIR QALSSAHLST SEIDVVEAHG TGTRLGDPIE
 351  AEALIATYGK EREDDRPLWL GSVKSNIGHT QAAAGVAGVI KMVMALQREL
 401  LPATLNVDEP TPHVQWEGGG VRLLTEPVPW SRGERPRRAG ISSFGISGTN
 451  AHVVLEEAPP EEDVPGPVAA EPEGVVPWVV SARTEEALSE QARRLGEFVA
 501  DTDPSTADVG WSLTTSRAIL EHRAVVVGRD RDALTAGLAA LAAGEESADV
 551  VAGVAGDVGP GPVLVFPGQG SQWVGMGAQL LDESPVFAAR IAECEQALSA
 601  YVDWSLSAVL RGDGSELSRV EVVQPVLWAV MVSLAAVWAD YGVTPAAVIG
 651  HSQGEMAAAC VAGALSLEDA ARVVAVRSDA LRQLMGQGDM ASLGASSEQA
 701  AELIGDRPGV CIAAVNGPSS TVISGPPEHV AAVVADAEER GLRARVIDVG
 751  YASHGPQIDQ LHDLLTDRLA DIRPATTDVA FYSTVTAERL TDTTALDTDY
 801  WVTNLRQPVR FADTIDALLA DGYRLFIEAS AHPVLGLGME ETIEQADIPA
 851  TVVPTLRRDH GDTTQLTRAA AHAFTAGATV DWRRWFPADP TPRTIDLPTY
 901  AFQRRSYWLP VDGVGDVRSA GLRRVEHSLL PAALGLADGA LVLTGRLAAS
 951  GGGGGWLADH AVAGTTLVPG AALVEWALRA ADEAGCPSLE ELTLQAPLVL
1001  PGSGGLQVQV VVGPADGQGG RREVRVFSRV DSDDEAAGQD EGWSCHATGV
1051  LSPEPGAVPD GLSGQWPPTG AEPLEISDLY EQAASAGYEY GPSFRGLRSV
1101  WRHGHNLLAE VELPEQAGAH DDFGIHPVLL DAALHPALLL DQNAPGEEQE
1151  PAQPALRLPF VWNGVSLWAT GAATVRVRLA PHGGGETDDS AGLRVTVADA
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1201 TGAPVLSVDS LALRPADPEL LRTAGRAGSG TNGLFTVEWT ALPPADVADH
1251 AAGDGWAVLG QDVPDWAGAD MPRHPDMASL SAALDEGTQA PAAVFVETTA
1301 TSHATPNTAA DVTLDASGRA VAERTLHLLR DWLAEPRLAE TRLVLITHHA
1351 VTTPADDDVN AAPLDVPAAA LWGLIRSAQA EHPDRFVLLD TDAKANTDPG
1401 PDTSTDHSTA SGTYRTVIAR ALATGEPQLA VRAGELLAPR LARAATPTPE
1451 TPTPETQPDT GSGSEAGAGS GSGPGATLDP DGTVLIAGGT GMMGGLVAEH
1501 LVRAWSVRHL LLVSRQGPDA PDARDLADRL VGLGATVRIV AADLTDGRAT
1551 ADLVASVDPA HPLTGVIHAA GVLDDAVVTA QTSDQLARVW AAKASVAANL
1601 DAATSELPLG LFLMFSSAAG VLGNAGQAGY AAANAFVDAL VGRRRATGLP
1651 GLSIAWGLWA RGSAMTRHLD DADLARLRAG GVKPLLDEQG LALLDAARAT
1701 AAHTSLVVAA GIDVRGLNRD DVPAILRDLA GRTRRRAAAD STVDQAALER
1751 RLTGLDEAER RAVVTDVVRE CVAAVLGHRS AADVRTEANF KDLGFDSLTA
1801 VQLRNRLSAA SGLRLPATLA FDHPTPQALA AYLGTRLSGR TATPVAPVAP
1851 SAAATDEPVA IVAMACKYPG GATSPEGLWD LVAEGVDAVG AFPTGRGWDL
1901 ERLFHPDPDH PGTSYADEGA FLPDAGDFDA AFFGINPREA LAMDPQQRLL
1951 LEASWEVLER AGIDPTTLKG TPTGTYVGVM YHDYAAGLAQ DAQLEGYSML
2001 AGSGSVVSGR VAYTLGLEGP AVTVDTACSS SLVSIHLAAQ ALRQGECTLA
2051 LAGGVTVMAT PEVFTGFSRQ RGLAPDGRCK PFAAAADGTG WGEGVGVLLL
2101 ERLSDARRHG RRVLGVVRGS AVNQDGASNG LTAPNGPSQE RVIRQALASG
2151 GLSSVDVDVV EGHGTGTTLG DPIEAQALLA TYGQGRPVDR PLWLGSVKSN
2201 IGHTQAAAGV AGVIKMVMAM RHGVVPASLH VDVPSPHVEW DSGAVRLAVE
2251 SVPWPEVEGR PRRAGVSSFG ASGTNAHVIV ESVPDGLGED SVSVSGEAPE
2301 TETDGRLVPW VVSARSPQAL RDQALRLRDA VAADSTVSVQ DVGWSLLKTR
2351 ALFEQRAVVV GRERAELLSG LAVLAAGEEH PAVTRSREDG VAASGAVVWL

2401 FSGQGSQLVG MGAGLYERFP VFAAAFDEVC GLLEGPLGVE AGGLREVVFR
2451 GPRERLDHTM WAQAGLFALQ VGLARLWESV GVRPDVVLGH SIGEIAAAHV
2501 AGVFDLADAC RVVGARARLM GGLPEGGAMC AVQATPAELA ADVDDSGVSV
2551 AAVNTPDSTV ISGPSGEVDR IAGVWRERGR KTKALSVSHA FHSALMEPML
2601 AEFTEAIREV KFTRPKVSLI SNVSGLEAGE EIASPEYWAR HVRQTVLFQP
2651 GIAQVASTAG VFVELGPGPV LTTAAQHTLD DVTDRHGPEP VLVSSLAGER
2701 PEESAFVEAM ARLHTAGVAV DWSVLFAGDR VPGLVELPTY AFQRERFWLS
2751 GRSGGGDAAT LGLVAAGHPL LGAAVEFADR GGCLLTGRLS RSGVSWLADH
2801 VVAGAVLVPG AALVEWALRA GDEVGCVTVE ELMLQAPLVV PEASGLRVQV
2851 VVEEAGEDGR RGVQIYSRPD ADAVSGDDSW ICHATGTLTP QHTDAPNDGL
2901 AGAWPAAGAV PVDLAGFYER VADAGYAYGP GFQGLRAVWR HGQDLLAEVV
2951 LPEAAGAHDG YGIHPALLDA TLHPALLLDW PGEVQDDDGK VWLPFTWNQV
3001 SLRAAGAATV RVRLSPGEHD EAEREVQVLV ADATGTDVLS VGSVTLRPAD
3051 IRQLQAVPGH DDGLFSVDWT PLPLSRTDVS QTDADGDADW VVLSDGVGSL
3101 ADVVSAAGGE APWAVVAPVG ASAGGGLAGF DRREGLDGRL VVERVLSLVQ
3151 EFLAAPELAE SRLLVLTRGA VATGGDGDGD VDASAAAVWG LVRSAQSENP
3201 GRFILLDVDM DVDVDVDMDV DVDVDVDVDV DGDGNGSDLD PDLNGRRLPH
3251 ATLRHAAEEL DEPQLALRDG QLLVPRLVRA TGGGLVVAPT DRAWRLDKGS
3301 AETLESVAPV AYPGVMEPLG PGQVRLGIHA AGINFRDVLV SLGMVPGQVG
3351 LGGEGAGVVT ETGPDVTHLS VGDRVMGVLH GSFGPTAVAD TRMVAPVPQG
3401 WDMRQAAAMP VAYLTAWYGL VELAGLKAGE RVLIHAATGG VGMAAVQIAR
3451 HLGAEVFATA SAAKHVVLEE MGIDAAHRAS SRDLAFEDTF RQATDGRGMD
3501 VVLNSLTGEF IDASLRLLGD GGRFLEMGKT DVRTPEEVAA EYPGVTYTVY
3551 DLVTDAGPDR IAVMMSELGE RFASGALDPL PVRSWPLDKA REAFRFMSQA

3601 KHTGKLVLDV PAPLDPDGTV LITGGTGALG QVVAEHLVRE WGVRHLLLAS

3651 RRGLDAPGSG ELADRLSDLG AEVTVAAADV SDPASVVELV GKTDPSHPLT

3701 GVVHAAGVLE DGIVTAQTPE GLARVWAAKA AAAANLHEAT REMRLGLFVV

3751 FSSAAATLGS PGQANYAAAN AYCDALMQRR RAAGQVGLSV GWGLWEAPDA

3801 KPGVAADAKP DVAADAKTGV AADGTPQGMT GTLSGTDVAR MARIGVKAMT

3851 SAHGLALLDA AHRHGRPHLV AVDLDTRVLA HKPAPALPAL LRAFAGDQGG

3901 QGGGRGGGRG GGPARPAAAT TRQNVDWAAK LSVLTAEEQH RTLLDLVRTH

3951 AAAVLGHAGT DAVRADAAFQ DLGFDSLTAV ELRNRLSAST GLRLPATFIF

4001 RHPTPSAIAD ELRAQLAPAG ADPAAPLFGE LDKLETVITG HAHDESTRTR

4051 LAARLQNLLW RLDDTSARSD HAAGASDADG DAVENRDLES ASDDELFELI

4101 DRELPS*

MonAVI, polyketide synthase multi-enzyme MONS6, housing extension module 9 Length: 1701 amino acids

1 MPGTNDMPGT EDKLRHYLKR VTADLGQTRQ RLRDVEERQR EPIAIVAMAC

51 RYPGGVASPE QLWDLVASRG DAIEEFPADR GWDVAGLYHP DPDHPGTTYV

101 REAGFLRDAA RFDADFFGIN PREALAADPQ QRVLLEVSWE LFERAGIDPA

151 TLKDTLTGVY AGVSSQDHMS GSRVPPEVEG YATTGTLSSV ISGRIAYTFG

201 LEGPAVTLDT ACSASLVAIH LACQALRQGD CGLAVAGGVT VLSTPTAFVE

251 FSRQRGLAPD GRCKPFAEAA DGTGFSEGVG LILLERLSDA RRNGHQVLGV

301 VRGSAVNQDG ASNGLTAPND VAQERVIRQA LTNARVTPDA VDAVEAHGTG

351 TTLGDPIEGN ALLATYGKDR PADRPLWLGS VKSNIGHTQA AAGVAGVIKM

401 VMAMRHGELP ASLHIDRPTP HVDWEGGGVR LLTDPVPWPR ADRPRRAGVS

451 SFGISGTNAH LIVEQAPAPP DTADDAPEGA ATPGASDGLV VPWVVSARSP

501 QALRDQALRL RDFAGDASRA PLTDVGWSLL RSRALFEQRA VVAGRERAEL

551 LAGLAALAAG EEHPAVTRSR EEAAVAASGD VVWLFSGQGS QLVGMGAGLY

601 ERFPVFAAAF DEVCGLLEGE LGVGSGGLRE VVFWGPRERL DHTVWAQAGL

651 FALQVGLARL WESVGVRPDV VLGHSIGEIA AAHVAGVFDL ADACRVVGAR

701 ARLMGGLPEG GAMCAVQATP AELAADVDGS SVSVAAVNTP DSTVISGPSG

751 EVDRIAGVWR ERGRKTKALS VSHAFHSALM EPMLGEFTEA IRGVKFRQPS

801 IPLMSNVSGE RAGEEITSPE YWARHVRQTV LFQPGVAQVA AEARAFVELG

851 PGPVLTAAAQ HTLDHITEPE GPEPVVTASL HPDRPDDVAF AHAMADLHVA

901 GISVDWSAYF PDDPAPRTVD LPTYAFQGRR FWLADIAAPE AVSSTDGEEA

951 GFWAAVEGAD FQALCDTLHL KDDEHRAALE TVFPALSAWR RERRERSIVD

1001 AWRYRVDWRR VELPTPVPGA GTGPDADTGL GAWLIVAPTH GSGTWPQACA

1051 RALEEAGAPV RIVEAGPHAD RADMADLVQA WRASCADDTT QLGGVLSLLA

1101 LAEAPATSSD TTSHTSTSCG TGSLASHGLT GTLTLLHGLL DAGVEAPLWC

1151 ATRGAVSCGD ADPLVSPSQA PVWGLGRVAA LEHPELWGGL VDLPADPESL

1201 DASALYAVLR GDGGEDQVAL RRGAVLGRRL VPDATPDVAP GSSPDVSGGA

1251 AHADATSGEW QPHGAVLVTG GVGHLADQVV RWLAASGAEH VVLLDTGPAN

1301 SRGPGRNDDL AAEAAEHGTE LTVLRSLSEL TDVSVRPIRT VIHTSLPGEL

1351 APLAEVTPDA LGAAVSAAAR LSELPGIGSV ETVLFFSSVT ASLGSREHGA

1401 YAAANAYLDA LAQRAGADAA SPRTVSVGWG IWDLPDDGDV ARGAAGLSRR

1451 QGLPPLEPQL ALGALRAALD GGKGHTLVAD IEWERFAPLF TLARPTRLLD

1501 GIPAAQRVLD ASSESAEASE NASALRRELT ALPVRERTGA LLDLVRKQVA

1551 AVLRYEPGQD VAPEKAFKDL GFDSLVVVEL RNRLRAATGL RLPATLVYDY

1601 PTPRTLAAHL LDRVLPDGGA AELPVAAHLD DLEAALTDLP ADDPRRKGLV

1651 RRLQTLLWKQ PDAMGAAGPA DEEEQAAPED LSTASADDMF ALIDREWGTR

1701 *

MonH, probable regulatory protein Length: 981 amino acids

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  1  VSGVERGVGS AGPVEQGDGL AGLVERAEAL AALRGAFDGS PGTGGSLVVL
 51  SGAVGTGKTA LLRAWADRIG ADADALVLTA TACRAERDLP LGVLEQLVRS
101  PGLPPASAER ALAWWDEEAS ATPGKTDANG TSANGTDANG TGAGQTGAGQ
151  AGVGQTGVGG EPVLAASALR GLCEVLRDLL AERPVVVAVD DAHHADAASL
201  QCLLSVVRRL RSARLHVLFT EYAHQKAQNA LLSSEFLHEP ALRRIRLEPL
251  SKAGVEALLA RHLDERTAQD LTPVVHGMSA GHPLLVRALA EDHRAAGGAG
301  EAYGRAVLSF LYRHETPVTQ VARAIAALGA HAGPGQVGRL LDVDAASVER
351  AVRQLTVAEV LHEGRLCHPA FAAAVLDGMP PEERRALHGR VADLLHEEGA
401  PATEVAAHLV AADRSDAPWA VPVFQEAAQL ALDEDQVETG VDYLRAAHQR
451  CRGAAQRAAV VGALADAEWR LDPAKVLRHL PDPAAMAPQT DPAALAPHTD
501  PAPTAAPTAA PTPTPIPTTP PLPTHLLWHG RVEEGLDAIG TLTGPGPNPA
551  GAPPMNPADL DTPWLWGAYL YPGHVKERLG SGALSPQRST PPAVTPELQG
601  AGTLMNDLLH GGERDATEAA ERALNRYRLG PRTIAVQTAA LAALTYRDRP
651  HRAAAWCDGL VAQADERNSP TWRALFTAWR ALLHLRQGDP AAAEQRAETA
701  LALLGSKGWG AAIGLPLAAA VQAKAALGDV DGAAALLERP VPQAVFQTRT
751  GLHYLAARGR YHLATGCHYA ALCDFYACGT RMSSWGVDLP ALEPWRLGAA
801  EAYLALGEGL LARQLVDGQL PLPTPDDGRT WGMTLRLRAA TSPAPARAEL
851  LDEAVAVLRE SGDTFELARA VADQAVAVRE GGEAERARLL ARKAELLARR
901  WGSAPAPATV PEPPERPGPA TPDAELTSAE RRVAELAAEG FTNREISRKL
951  CVTVSTVEQH LTRIYRKLDV RRLDLQAALG *
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MonCI, flavin-dependent epoxidase Length: 496 amino acids

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  1  VTTTRPAHAV VLGASMAGTL AAHVLARHVD AVTVVERDAL PEEPQHRKGV
 51  PQARHAHLLW SNGARLIEEM LPGTTDRLLA AGARRLGFPE DLVTLTGQGW
101  QHRFPATQFA LVASRPLLDL TVRQQALGAD NITVRQRTEA VELTGSGGGS
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151 GGRVTGVVVR DLDSGRQEQL EADLVIDATG RGSRLKQWLA ALGVPALEED

201 VVDAGVAYAT RLFKAPPGAT THFPAVNIAA DDRVREPGRF GVVYPIEGGR

251 WLATLSCTRG AQLPTHEDEF IPFAENLNHP ILADLLRDAE PLTPVFGSRS

301 GANRRLYPER LEQWPDGLLV IGDSLTAFNP IYGHGMSSAA RCATTIDREF

351 ERSVQEGTGS ARAGTRALQK AIGAAVDDPW ILAATKDIDY VNCRVSATDP

401 RLIGVDTEQR LRFAEAITAA SIRSPKASEI VTDVMSLNAP QAELGSNRFL

451 MAMRADERLP ELTAPPFLPE ELAVVGLDAA TISPTPTPTP TAAVRS

MonBII, carbon-carbon double bond isomerase Length: 141 amino acids

1 MPDEAARKQM AVDYAERINA GDIEGVLDLF TDDIVFEDPV GRPPMVGKDD

51 LRRHLELAVS CGTHEVPDPP MTSMDDRFVV TPTTVTVQRP RPMTFRIVGI

101 VELDEHGLGR RVQAFWGVTD VTMDDPAGPA DTTHPEGIRA *

MonBI, carbon-carbon double bond isomerase Length: 144 amino acids

1 MNEFARKKRA LEHSRRINAG DLDAIIDLYA PDAVLEDPVG LPPVTGHDAL

51 RAHYEPLLAA HLREEAAEPV AGQDATHALI QISSVMDYLP VGPLYAERGW

101 LKAPDAPGTA RIHRTAMLVI RMDASGLIRH LKSYWGTSDL TVLG

MonAVIII, polyketide synthase multi-enzyme MONS8, housing extension modules 11 and 12 Length: 3754 amino acids

1 MSNEEKLLDH LKWVTAELRQ ARQRLHDKES TEPVAIVGMA CRYPGGARSA

51 EDLWELVRDG GDAVAGFPDD RGWDLESLYH PDPEHPATSY VRDGAFLYDA

101 GHFDAEFFGI SPREATAMDP QQRLLLETAW EAIEHAGMNP HALKGSDTGV

151 FTGVSAHDYL TLISQTASDV EGYIGTGNLG SVVSGRISYT VGLEGPAVTV

201 DTACSSSLVA IHLASQALRQ GECSLALAGG STVMATPGSF TEFSRQRGLA

251 PDGRCKPFAA AADGTGWGEG AGVVALELLS EARRRGHKVL AVIRGSATNQ

301 DGTSNGLAAP NGPSQERVIR AALANARLSA EDIDAVEAHG TGTTLGDPIE

351 AQALIATYGQ GRPEDRPLWL GSVKSNIGHT QAAAGVAGVI KMVMAMRNGL

401 LPTSLHIDAP SPHVQWEQGS VRLLSEPVDW PAERTRRAGI SAFGISGTNA

451 HLILEEAPPE EDAPGPVAAE PGGVVPWVVS GRTPDALREQ ARRLGEFAAG

501 LADASVSEVG WSLATTRALF DQRAVVVGRD LAQAGASLEA LAAGEASADV

551 VAGVAGDVGP GPVLVFPGQG SQWVGMGAQL LDESPVFAAR IAECEQALSA

601 HVDWSLSDVL RGDGSELSRV EVVQPVLWAV MVSLAAVWAD YGITPAAVIG

651 HSQGEMAAAC VAGALSLEDA ARIVAVRSDA LRQLQGHGDM ASLSTGAEQA

701 AELIGDRPGV VVAAVNGPSS TVISGPPEHV AAVVADAEAQ GLRARVIDVR

751 YASHGPQIDQ LHDLLTDRLA DIQPTTTDVA FYSTVTAERL DDTTALDTAY

801 WVTNLRQPVR FADTIEALLA DGYRLFIEAS PHPVLNLGIQ ETIEQQAGAA

851 GTAVTIPTLR RDHGDTTQLT RAAAHAFTAG APVDWRRWFP ADPTPRTVDL

901 PTYAFQHKHY WVEPPAAVAA VGGGHDPVEA RVWQAIEDLD IDALAGSLEI

951 EGQAESVGAL ESALPVLSAW RRRHREQSTV DSWRYQVTWK HLPDVPAPEL

1001 SGAWLLLVPA AHADHPAVLA TAQTLTAHGG EVRRHVVDAR AMERTELAQE

1051 LRVLMDGAAF AGVVNLLALD EEPHPEHSAV PAGLAATTAL VQALADNGAD

1101 IAVRTLTQGA VSTSAGDALT HPVQAQVWGL GRVAALEYPR LWGGLVDLPA

1151 RIDHQTLARL AAALVPQDED QISIRPSGVH ARRLAHAPAN TVGSGLGWRP

1201 DGTTLITGGT GGIGAVLARW LARAGAPHLL LTSRRGPDAP GAQELAAELT

1251 ELGAAVTVTA CDVGDREQVR RLIDDVPAEH PLTAVIHAAG VPNYIGLGDV

1301 SGAELDEVLR PKALAAHHLH ELTRELPLSA FVMFSSGAGV WGSGQQGAYG

1351 AANHFLDALA EHRRAEGLPA TSIAWGPWAE AGMAADQAAL TFFSRFGLHP

1401 LSPELCVKAL QQALDAGETT LTVANFDWAQ FTSTFTAQRP SPLLADLPEN

1451 RRASAPAAQQ EDATEASSLQ QELTEAKPAQ QRQLLLQHVR SQAAATLGHS

1501 DVDAVPATKP FQELGFDSLT AVELRNRLNK STGLTLPTTV VFDHPTPDAL

1551	TDVLRAELSG	DAAASADPVR	AAGASRGAAD	DEPIAIVGMA	CRYPGDVRSA
1601	EELWDLVAAG	KDAMGAFPDD	RGWDLETLYD	PDPESRGTSY	VREGGFLYDA
1651	GDFDAGFFGI	SPREAVAMDP	QQRLLLETAW	EAIERAGLDR	ETLKGSDAGV
1701	FTGLTIFDYL	ALVGEQPTEV	EGYIGTGNLG	CVASGRVSYV	LGLEGPAMTI
1751	DTGCSSSLVA	IHQAAHALRQ	GECSLALAGG	ATVMATPGSF	VEFSLQRGLA
1801	KDGRCKPFAA	AADGTGWAEG	VGLVVLERLS	EARRNGHNVL	AVIRGSAINQ
1851	DGTSNGLTAP	NGQAQQRVIR	QALANARLSA	EDVDAVEAHG	TGTMLGDPIE
1901	ASALVATYGK	ERPADRPLWL	GSIKSNIGHA	QASAGVAGVI	KMVMALRNEQ
1951	LPASLHIDAP	TPHVDWDGSG	VRLLSEPVSW	PRGERPRRAG	VSAFGISGTN
2001	AHLILEQAPD	APEPVTAPAE	DAAAPAGVVP	WVVSARGEEA	LRAQARLLAD
2051	RATADPRLAS	PLDVGWSLVK	TRSVFENRAV	VVGKDRQTLL	AGLRSLAAGE
2101	PSPDVVEGAV	QGASGAGPVL	VFPGQGSQWV	GMGAQLLDES	PVFAARIAEC
2151	ERALSAHVDW	SLSAVLRGDG	SELSRVEVVQ	PVLWAVMVSL	ASVWADYGIT
2201	PAAVIGHSQG	EMAAACVAGA	LSLEDAARIV	AVRSDALRQL	MGQGDMASLG
2251	AGSEQVAELI	GDRPGVCVAA	VNGPSSTVIS	GPPEHVAAVV	ADAEARGLRA
2301	RVIDVGYASH	GPQIDQLHDL	LTERLADIRP	TTTDVAFYST	VTAERLDDTT
2351	TLDTDYWVTN	LRQPVRFADT	IEALLADGYR	LFIEASPHPV	LNLGMEETIE
2401	RADMPATVVP	TLRRDHGDAA	QLTRAAAQAF	GAGAEVDWTG	WFPAVPLPRV
2451	VDLPTYAFQR	ERFWLEGRRG	LAGDPAGLGL	ASAGHPLLGA	AVELADGGSH
2501	LLTGRISPRD	QAWLAEHRVM	DTVLLPGSAF	VELALQAAVR	AGCAELAELT
2551	LHTPLAFGDE	GAGAVDVQVV	VGSVAEDGRR	PVTVHSRPTG	EGEEAVWTRH
2601	AAGVVAPPGP	DAGDASFGGT	WPPPGATPVG	EQDPYGELAS	YGYDFGPGSQ
2651	GLVSAWRLGD	DLFAEVALPE	AESGRADRYQ	VHPVLLDATL	HALILDAVTS
2701	SADTDQVLLP	FSWSGLRVHA	PGAEKLRVRI	ARTAPDQLAL	TAVDGGGGGE

2751 PVLTLESLTV RPVAAHQIAG ARAADRDALF RLVWMEVAAR AEETGGGAPR

2801 AAVLAPVESG PMGGTSAGAL ADALSDALAA GPVWDTFGAL RDGVAAGGEA

2851 PDVVLAVCAA PGAGAGAVAD ADGRGGDPAG YARLATVSLL SLLKEWVDDP

2901 AFAATRLVVV TRGAVAARPG ETAGDLAGAS LWGLVRSAQA ENPGRLTLLD

2951 VDGLESSPAT LTGVLASGEP ELALRDGRAY VPRLVRDDAS VRLVPPVGSL

3001 TWRLARCQEA GGGQQLSLVD APEAGRALEP HEVRVAVRAA APGPLTAGQV

3051 EGAGVVTEVG GEVGSVAVGD RVMGLFDAVG PVAVTDAALL MPVPAGWSWA

3101 QAAGSLGAYV SAYHVLADVV APRGGETLLV GEETGSVGRA VLRLALAGRW

3151 RVEAVDGAST ADDSGAERAA DVTLRHEGAL VVHRAGGRPD EGQAVVPPEP

3201 GRVREILAEL TELTELAEIT ESAEPGLPAE RGDSRALTPL DITVWDIRQA

3251 PAAMAAPPSA GTTVFSLPPA FDPEGTVLVT GGTGALGSLT ARHLVERYGA

3301 RHLLLSSRRG ADAPGALELA ADLSALGARV TFAACDPGDR DEAAALLAAV

3351 PSDHPLTAVF HCAGTVNDAV VQNLTAEQVE EVMRVKADAA WHLHELTRDA

3401 DLSAFVLYSS VAGLLGGPGQ GSYTAANAFL DALARHRHDG GAAATSLAWG

3451 YWELASGMSG RLTDADRARH ARAGVVGLGA DEGLALLDAA WAGGLPLYAP

3501 VRLDLARMRR QAQSHPAPAL LRDLVRGGSK SGGGAVSAGA AALLKSLGAM

3551 SDPEREEALL DLVCTHIAAV LGYDAATPVN ATQGLRELGF DSLTAVELRN

3601 RLSAATGLKL PATFVFDHPN PAELAAQLRQ ELAPRAADPL ADVLAEFERI

3651 EDSLLSVSSK DGSARAELAG RLRATLARLD APQDTAGEVA VATRTRIQDA

3701 SADEIFAFID RDLGRDGASG QGNGQPTGQG NGHGNGNGNG NGNGHGQAVE

3751 GQR*

MonAVII, polyketide synthase multi-enzyme MONS7, housing extension module 10 Length: 1642 amino acids

1 MAHTEEKLLE YLKRVTADLR QTERRLQDVE SAGHEPVAVI GMACRLPGGV

51 RSPEEFWELV STGGDAVAPL PGNRNWDLDS LYDPDPESTG TSYVREGGFV

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101  YDAGDFDPTF FGIGPTEAAA MAPQQRLALE TAWEAIERAG IDPLSLRSSD
151  TSTFIGCDGL DYALGASEVP EGTAGYFTIG NSGSVTSGRV AYTLGLEGPA
201  VTVDTACSSS LVSLHLATQA LRTQECSLAL AGGTYVMSSP APLIGFSELR
251  GLAPDGRCKP FSASSDGMGM AEGTGVVLLE RLSDARRKGH KVLAVIRGSA
301  INQDGASNGL TAPNGPAQER VIRAALANAR LAPEDIDAVE AHGTGTTLGD
351  PIEAGALISA YGRERPEDRP LWVGAVKSNI GHTQIAAGVA GVIKMVLALR
401  HDLLPAILHV DAPSPHVEWD GSGLRLLTDP VKWPRGERPR RAGVSSFGFS
451  GTNAHLILEE APPEEEDVPG SVAEEPGGVV PWVVSGRTPD ALRAQARRLG
501  EFAAGPADAS AADVGWSLTT TRSVFEHRAV VVGRDRDALT AGLGALAAGE
551  ASAGVVAGVA GDVGPGPVLV FPGQGSQWVG MGAQLLDESP VFAARIAECE
601  RALSAYVDWS LSAVLRGDGS ELSRVEVVQP VLWAVMVSLA AVWADYGVTP
651  AAVIGHSQGE MAAACVAGAL SLEDAARIVA VRSDALRRLQ GHGDMASLST
701  GAEQAAELIG DRPGVVVAAV NGPSSTVISG PPEHVAAVVA DAEARGLRAR
751  VIDVGYASHG PQIDQLHDLL TERLADIRPA NTDVAFYSTV TAERLTDTTA
801  LDTDYWVTNL RQPVRFADTI EALLADGYRL FIEASAHPVL GLGMEETIEQ
851  ADIPATVVPT LRRDHGDTTQ LTRAAAHAFT AGAPVDWRRW FPADPTPRTV
901  DLPTYAFQHQ HYWLERSASA SGAVSGEQSA AEAQLWHAVE ELDLGLLAET
951  LGSEEGSEEA VRALEPALPV LKGWRRRHQD QATIDSWRYR VTWKQRSDGP
1001  APELGGDWLL FVPADKAEHP AVRATAEALS EHGAAAVRLH PVETGRAGRQ
1051  ELAAVDTAGL AGIVNLLALD EEPHPEHPAV PAGLAATTAL LQALGDNGTT
1101  APLHTVTQGA VSTGATDPLT HPLQAHVWGL GRVAALEHPR LWAGLVDLPA
1151  RIDRHTLPRL AAALLPQDDE DQTAVRPTGI HHRRLTHAVG SIQNPVHSEA
1201  TWRPRGTTLI TGGTGGIGAV LARWLARQGA PRLHLTSRRG PDAPGARELA
1251  AELDGLGTAV TITACDVSDP RQLSGLIDDM PAEHPLTAVI HAAGMTDLTA
```

1301 IGDLTTARLG EVLGSKSDAA WNLHELTRDL DLSAFVMFSS GAGVWGSGQQ

1351 GAYGAANHFL DALAEHRRAQ GLPATSIAWG PWAEAGMSAD PESLTYFKRF

1401 GLLPIAPDLC VKALHQAVDA GDATLTVANF DWAKFTPTFT AQRPSPFLDD

1451 LPENQREAEQ TGTAAETSAF REELAKTPAS QRLGFLVQQV RTYAAATLGR

1501 TVEDIPAAKP FQELGFDSLT AVQLRNQLNT TTGLSLPATV IFDHPTPEAL

1551 ATHLRGQLGD GAEVAGEGDV LAALDKWDTA FGAAEVDEAA RRRIVGRLQV

1601 LVSKWSPAQD GPEGTDSAHA DLEAASADDI FDLISSEFGK S*

MonD, cytochrome P450 hydroxylase Length: 431 amino acids

1 VGLTVGPDNA KRGIVPITDS KPAATFPDLV DPSFWARPHA ERVALFEEMR

51 GLPRPAFIRQ NMPGVPWTFG YHALVKYADI VEVSRRPQDF SSNGATTIIG

101 LPPELDEYYG SMINMDNPEH SRLRRIVSRS FGRNMIPEFE AVATRTARRI

151 IDELIARGPG DFIRPVAAEM PIAVLSDMMG IPAEDHDFLF DRSNTIVGPL

201 DPDYVPDRAD SERAVIEASR ELGDYIAGLR AERLAAPGND LITKLVQVQA

251 DGEQLTRQEL VSFFILLVIA GMETTRNAIS HALVLLTEHP EQKQLLLSDF

301 DTHAPNAVEE ILRVSTPINW MRRVATRDCD MNGHRFRRGD RIFLFYWSGN

351 RDESVFPDPY RFDITRGTNA HVTFGAVGPH VCLGAHLARM EITVLYRELL

401 AALPQIHAVG QPRRLDSSFI EGIKHLHCAF *

MonRI, probable activator protein Length: 268 amino acids

1 VRYEMLGPLR IKDGNDYATI NAQKVEIVLT VLLIRADRVV SLEQLMREIW

51 GEDLPRRATA GLHVYISQLR KFLKVPGSAG NPVETRAPGY VLHKRDDDQI

101 DAQIFPELVD VGRSLLREKR FDEAASCFGQ ALALWRGPIL GQGGNGPGTN

151 GPIIDGFSTW LTEIRLECQE MLVECQLQLG RHREAVGMLY ALTAENPMCE

201 AFYRQLMLAL YRSERQADAL KVYQSVRKTL NDELGLEPGR PLQELQRAIL

251 AGDMHLMSPP PLALSGR*

MonAX, thioesterase Length: 278 amino acids

```
  1  LSAFLAKGKI LSAFPPPDMS DPWIRRFRPR PEAVVRLVCF PHAGGSASYY
 51  HPLAQSPTLP TDSEVLAVQY PGRQDRRRER LLDDIGELAD LITDALGPFD
101  DRPLAFFGHS MGAVLAYEVA QRLRERTGKQ PCRLFVSGRR APSRFRRGTV
151  HLLDDTELAA ELRRAGGTDP RFLDDEELLA EIIPVVRNDY RAVELYRWNP
201  SPPLSCPITA LVGDRDPQAP LDEVEAWQQH TEGPFDLKVF AGGHFYLNTH
251  QQGVTEVISK ALADSAQQRA TARGNAR*
```

ORF29, a homologue of CapK involved in cell wall biosynthesis Length: 428 amino acids

```
  1  LADLVAHARS ASPYYRELYH GLPERIEDPT LLPVTDKKQL MDHFDDWPTD
 51  RDITFEKVRA FTDDPELIGR RFLGRYLVAT TSGTSGRRGL FVLDDRYMNV
101  SSAVSSRVLA SWLGPLGIAR AVVHGGRFAQ LVATEGHYVG FAGYSRLRQD
151  GEARSKLVRA FSVHEPMSRL VAELNEYRPA FVIGYASTIM LFTAEQEAGR
201  LHIDPVLVEP AGETMTESDT DRIAAAFGAK VRTMYSATEC TYLSHGCAEG
251  WYHVNDDWAV LEPVDADHRP TPPGEFSHTT LISNLANRVQ PFLRYDLGDS
301  VMLRPDPCPC GTPSPAIRVQ GRSGDILTFP SGRGDDVSLA PLAFSSLFDR
351  MPGVELFQIE QTAPSTLRVR VVQAPGADAD HVWQRAHDGL THLLADNKLD
401  NVTVERGEEP PRQASGGKYR TIIPLAA*
```

LipB, lipase B Length: 338 amino acids

```
  1  VKVPVEVTVR LSSWLGGLVA AVLAATVLPA SAASAADVSS PPLEIPAAEL
 51  AKALHCGTEL GDLRDAGDKP TVLFVPGTGL KGEENYAWNY MAELKKKGYQ
101  SCWVDSPGRG LRDMQESVEY VVYATRAIQE ATGRKVDLVG HSQGGLLTAW
151  ALRFWPDLPG KVDDMVTLGS PFQGTRLASP CRPIAEVAGC PASVLQFARD
201  SNWSKALGAD GTPMPAGPSY TTIYSYADES VVADGEAPSL PGAHRIGVQD
```

```
251  ICPGRPWPTH IAMVVDQVSY DLVADAIEHP GPADTSRIDR AHCAKPVMPL
301  NSQEAVDALP GLLNFPIELL IHSQPWVDEE PPLRPYAR
```

ORF31, putative ion pump Length: 309 amino acids

```
  1  MGHDHGPSAG AAGGTLSGTY RKRLLWTIGI SGSITVIQVV GALLSGSLAL
 51  LADAAHSLTD AVGVSLALGA ITLAQRAPTP RRTFGFCRVE IFSAVLNALL
101  LVVIFAWVLW SAIGRFSEPV EVKGGLMFVV ALGGLAANLV GLWLLRDAKE
151  KSLNLRGAYL EVLGDALGSV AVIVGGLVIL LTGWQAADPI ASIVIGLLIV
201  PRAYGLLRDS LHVLLEATPQ DVDLGEVRRH LLEERGVVAV HDLHGWTVTS
251  GMPVLTAHVV VTEEALASGY GELLGRLQRC VGGHFDVAHS TIQLEPEGHV
301  EEDGALHT*
```

ORF32, hypothetical membrane protein Length: 364 amino acids

```
  1  MTRALTLHDW IVAGIAVVAG VVAGLLLRAL LRWLGERASK TRWSGDDVIV
 51  DALRTLVPCA AITAGLAAAA GALPLTPRTG RNVTMTLTAL LILAATLTAA
101  RIVTGLVKAV AQSRSGVAGS ATIFVNITRV VVLAMGFLIV LQTLGISIAP
151  LLTALGVGGL AVALALQDTL ANLFAGVHIL AAKTVQPGDY IQLSSGEEGY
201  VVDINWRNTT VRQLSNNLVI IPNAKLAGTN MTNYSRPEQE LSIMVQVGVS
251  YDSDLEQVEK VTTEVVDEVM AEITGAVPDH EAAIRFHTFG DSRISFTVIL
301  GVGEFSDQYR IKHEFIKRLH QRYRAEGIRV PAPVRTVRVQ QGELPPPLGI
351  PHQRDTSTQA RLH*
```

AmtA, glycine amidinotransferase (partial coding sequence) Length: 131 amino acids

```
  1  MSPVNSHNEW DPLEEIIVGR LEGATIPSSH PVVACNIPTW AARLQGLAAG
 51  FEYPQRLIEP AQQELDQFIA LLQSLDVTVR RPAAVDHKHR FGTPDWQSRG
101  FCNSCPRDSM LVVGDEIIET PMAWPCRCFE T
```

CLAIMS:

1. A DNA sequence which is (a) at least part of the sequence set out in the appended sequence listing; or (b) a variant of a sequence (a) which encodes a polypeptide which is at least 80%, preferably at least 90%, identical with the corresponding peptide as set out in table II; provided that it is not a sequence encoding all or part of the polypeptide consisting of amino acids 1-920 encoded by *mon AI* as set out in table II.

2. A DNA sequence according to claim 1 comprising the complete monensin gene cluster or a variant thereof.

3. A DNA sequence encoding at least part of at least one polypeptide which is necessary for the biosynthesis of monensin, and which is encoded by DNA included in the appended sequence listing or an allele, mutation or other variant thereof; provided that said polypeptide is not all or part of amino acids 1-920 encoded by *mon AI* as set out in table II.

4. A DNA sequence according to claim 3 which comprises at least part of one or more of the following genes: *mon BI, mon BII, mon CI, mon CII, mon H, mon RI, mon RII, mon T, mon AIX* and *mon AX*.

5. A DNA sequence according to claim 4 comprising all of the genes listed therein or an allele, mutation or other variant thereof.

6. A DNA sequence according to claim 3 encoding at least part of one or more of the polypeptides set out below, said polypeptide having the amino acid sequence as set out in the appended sequence data or being a variant thereof having the specified activity:

peptide	activity
mon CII	epoxyhydrolase/cyclase
mon E	S-adenosylmethionine-dependent methyltransferase
mon T	monensin resistance gene
mon RII	repressor protein
mon AIX	thioesterase
mon AI	polyketide synthase multienzyme
mon AII	polyketide synthase multienzyme
mon AIII	polyketide synthase multienzyme
mon AIV	polyketide synthase multienzyme
mon AV	polyketide synthase multienzyme
mon AVI	polyketide synthase multienzyme
mon AVII	polyketide synthase multienzyme
mon AVIII	polyketide synthase multienzyme
mon H	regulatory protein
mon CI	flavin-dependent epoxidase
mon BII	carbon-carbon double bond isomerase

mon BI carbon-carbon double bond isomerase

mon D cytochrome P450 hydroxylase

mon RI activator protein

mon AX thioesterase

7. A DNA sequence according to claim 6 encoding a single enzyme activity of a multienzyme encoded by any of *mon AI-mon AVIII* or a variant or part thereof.

8. A DNA sequence according to any preceding claim encoding any one or more of the domains as set out in Table I or a variant or part thereof.

9. A DNA sequence according to any preceding claim which has a length of at least 30, preferably at least 60, bases.

10. A recombinant cloning or expression vector comprising a DNA sequence according to any preceding claim.

11. A transformant host cell which has been transformed to contain a DNA sequence according to any of claims 1-9 and which is capable of expressing a corresponding polypeptide.

12. A hybridisation probe which is a DNA sequence according to any of claims 1-9.

13. Use of a probe according to claim 12 to detect a PKS cluster, optionally followed by isolation of the detected cluster.

14. Use of a probe according to claim 12 which encodes at least part of a polypeptide having a known function to detect genes encoding polypeptides having analogous function.

15. Use according to claim 14 wherein the polypeptide of known function is AT of module 5 or the regulatory protein encoded by *mon RI*.

16. A hybridization probe comprising a polynucleotide which binds specifically to a region of the monensin gene cluster selected from *mon BI, mon BII, mon CI, mon CII, mon H, mon RI, mon RII, mon T, mon AIX* and *mon AX*.

17. Use of a probe according to claim 16 in a method of detecting the presence of a gene cluster which governs the synthesis of a polyether, and optionally isolating a gene cluster detected thereby.

18. Use of a probe according to claim 12 which comprise a polynucleotide which binds specifically to a gene responsible for levels of activity of the monensin gene cluster, in a method of detecting an analogous gene in a gene cluster for biosynthesis of another polyketide, optionally followed by a step of manipulating the gene detected thereby to alter the level of expression of said other polyketide.

19. Use according to claim 18 wherein the gene is a regulatory gene, resistance gene or thioesterase gene.

20. Use of the *mon RI* gene or variant and a monensin promoter to control expression of a heterologous gene in *S. cinnamonensis*.

21. Use of a portion of the monensin gene cluster encoding a polypeptide having chain terminating activity, preferably comprising at least one of *mon AIX* and *mon AX* or a mutant, allele or other variant thereof encoding a polypeptide having chain terminating activity, to effect chain release of a peptide other than monensin.

22. Use of a portion of the monensin gene cluster encoding a polypeptide having carbon-carbon double bond isomerase activity, preferably comprising at least one of

mon BI and *mon BII* or a mutant, allele or other variant thereof having isomerase activity to provide a desired stereochemical outcome in the synthesis of a polyketide other than monensin.

23. A polypeptide encoded by a portion of the monensin gene cluster, preferably comprising at least one of *mon BI* and *mon BII* or a mutant, allele or other variant thereof, having carbon-carbon double bond isomerase activity, or at least one of *mon AIX* and *mon AX* or a mutant, allele or other variant thereof having chain terminating activity.

24. An epoxidase enzyme encoded by *mon CI* or a derivative or variant thereof having epoxidase activity.

25. A cyclase enzyme encoded by *mon CII* or a derivative or variant thereof having cyclase activity.

26. Use of a portion of the monensin gene cluster encoding a peptide having epoxidase or cyclase activity, preferably comprising *mon CI* or *mon CII* or a mutant, allele or other variant thereof encoding a polypeptide having epoxidase or cyclase activity to provide a said activity in the biosynthesis of a polypeptide other than monensin.

27. A process for producing a polyketide containing a desired starter unit comprising providing a PKS gene having a loading module and a plurality of extension modules, wherein the loading module includes a KS_q domain derived from a KS domain of a monensin extension module.

28. A process according to claim 27 wherein the KS_q domain is derived from KS of module 5 of monensin.

29. A process according to claim 27 or claim 28 wherein the starter unit also includes an AT_q domain derived from an AT domain which is naturally associated with the KS domain.

30. A DNA sequence comprising DNA encoding at least one PKS loading module and a plurality of PKS extension modules, and which can be expressed to produce a polyketide; wherein at least one of said modules or at least one domain thereof is a monensin module or domain or a variant thereof and is contiguous to a further one of said modules or a domain to which it is not naturally contiguous; provided that the sequence is not an ery loading module, the first and second extension modules of the ery PKS and the ery chain-terminating thioesterase in which the DNA encoding AT of the first extension module has been substituted by DNA encoding an ethyl malonyl-CoA

AT from the monensin gene cluster.

31. A DNA sequence according to claim 30 wherein said further module or domain is also a monensin module or domain or variant thereof.

32. A DNA sequence according to claim 30 wherein said further module or domain is a module or domain of a PKS of a polyketide other than monensin or a variant thereof.

33. A DNA sequence according to claim 30, 31 or 32 wherein said loading module is adapted to load a starter unit other than a starter unit normally received by the adjacent extension module.

34. A DNA sequence according to claim 33 wherein said loading module is derived from a monensin extension module or variant thereof.

35. A polyketide synthase encoded by the DNA sequence of any of claims 30-34.

36. A polyketide compound as produced by a synthase according to claim 35.

37. A vector containing a DNA sequence of any of claims 30-34.

38. A transformant cell transformed to contain a DNA sequence of any of claims 30-34.

39. A method of producing *S. cinnamonensis* capable of enhanced levels of production of monensin comprising engineering it to overexpress the *mon RI* gene.

40. A method according to claim 39 wherein said engineering comprises introducing at least one additional copy of the *mon RI* gene as shown in the appended sequence data or a variant thereof.

41. *S. cinnamonensis* containing multiple copies of the *mon RI* gene as shown in the appended sequence data and/or variant(s) thereof.

42. A method of producing monensin comprising culturing the organism of claim 41 and/or an organism produced by the method of claim 39 or claim 40.

43. A process for expressing a gene heterologous to *S. cinnamonensis* comprising transforming *S. cinnamonensis* with DNA encoding a heterologous gene and expressing said

gene under control of the activator gene *mon RI* or actII/orf4.

44. A process according to claim 43 wherein said heterologous gene is a PKS gene.

45. 13-Propyl erythromycin A.

POLYKETIDES AND THEIR SYNTHESIS

ABSTRACT

The complete sequence of the gene cluster for the monensin type I polyketide synthase, from *S. cinnamonensis*, is provided. Thus variant polyketides containing monensin-derived elements can be genetically engineered. Furthermore there are novel features, e.g. a regulatory protein *mon RI*, which are of wide utility.

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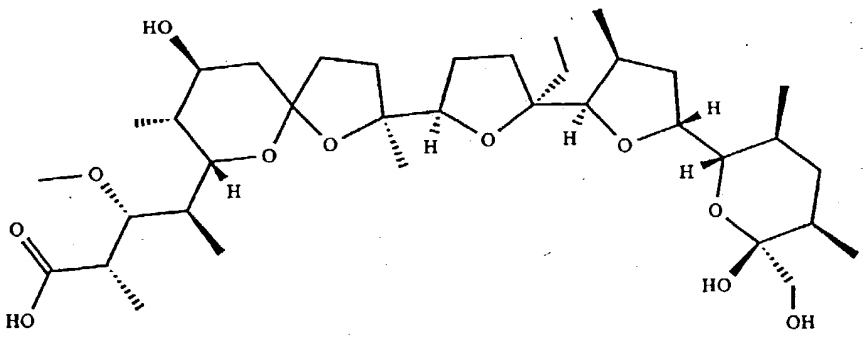

monensin A : R = ethyl
monensin B : R = methyl

Fig 1

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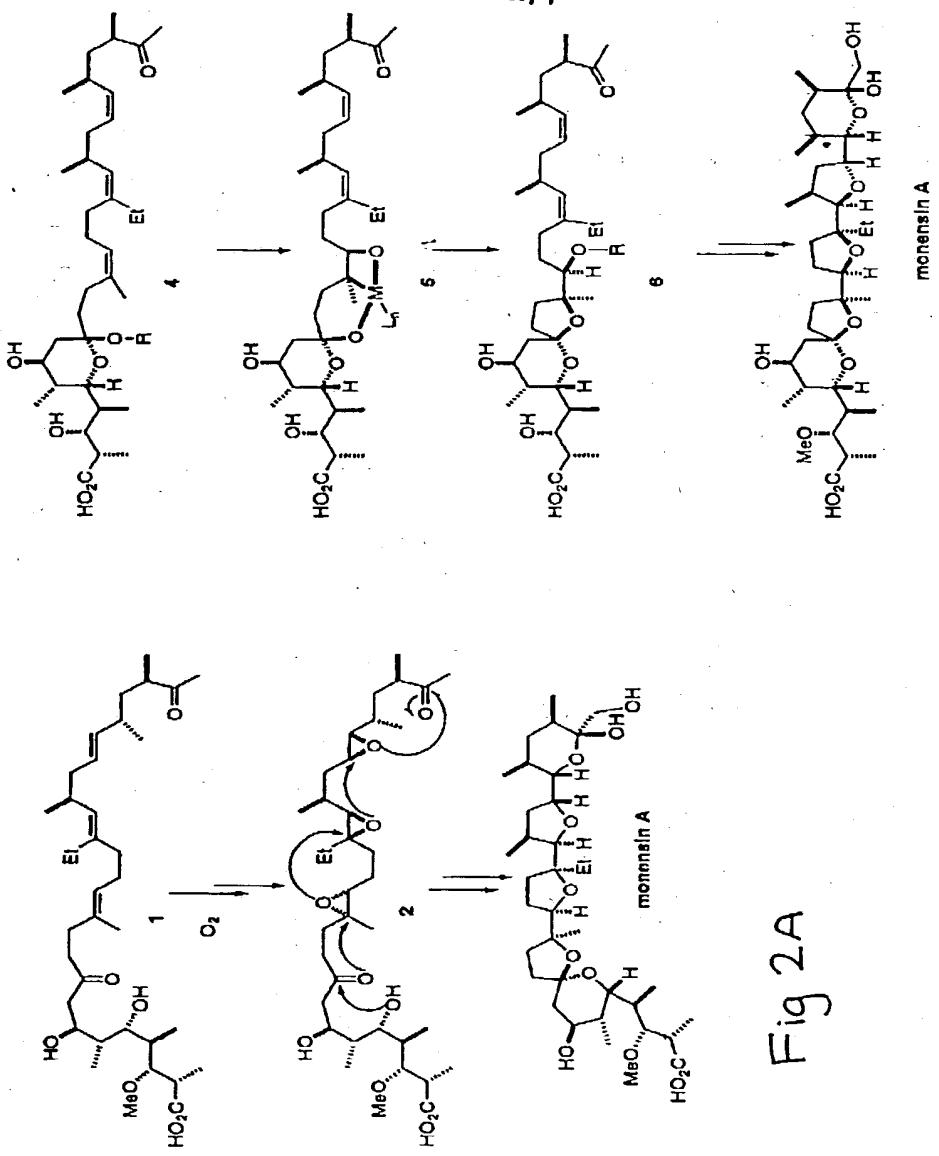

Fig 2A

Fig 2B

Figure 2. Proposed mechanisms for monensin biosynthesis.

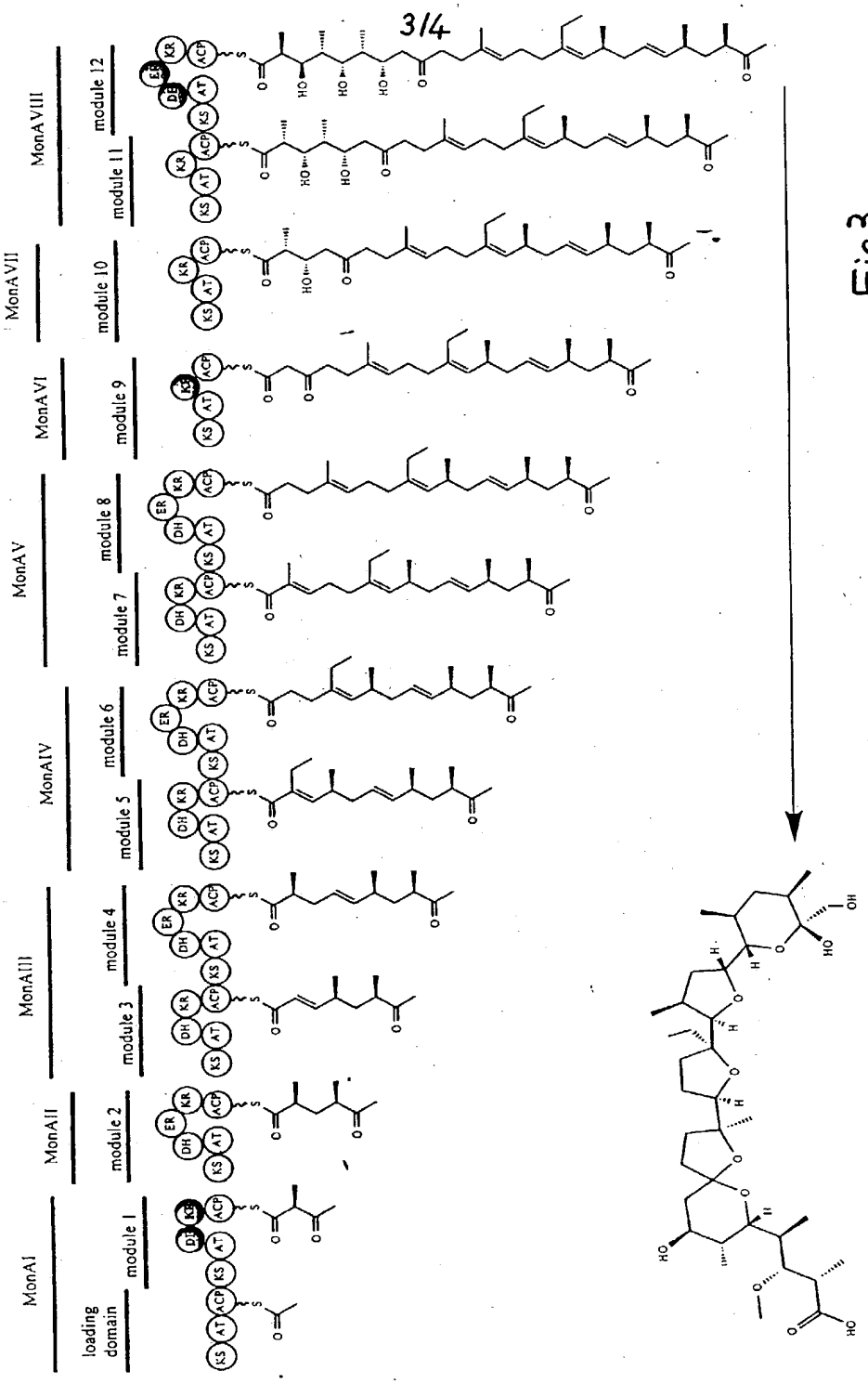

Fig3

Proposed organisation of the monensin PKS

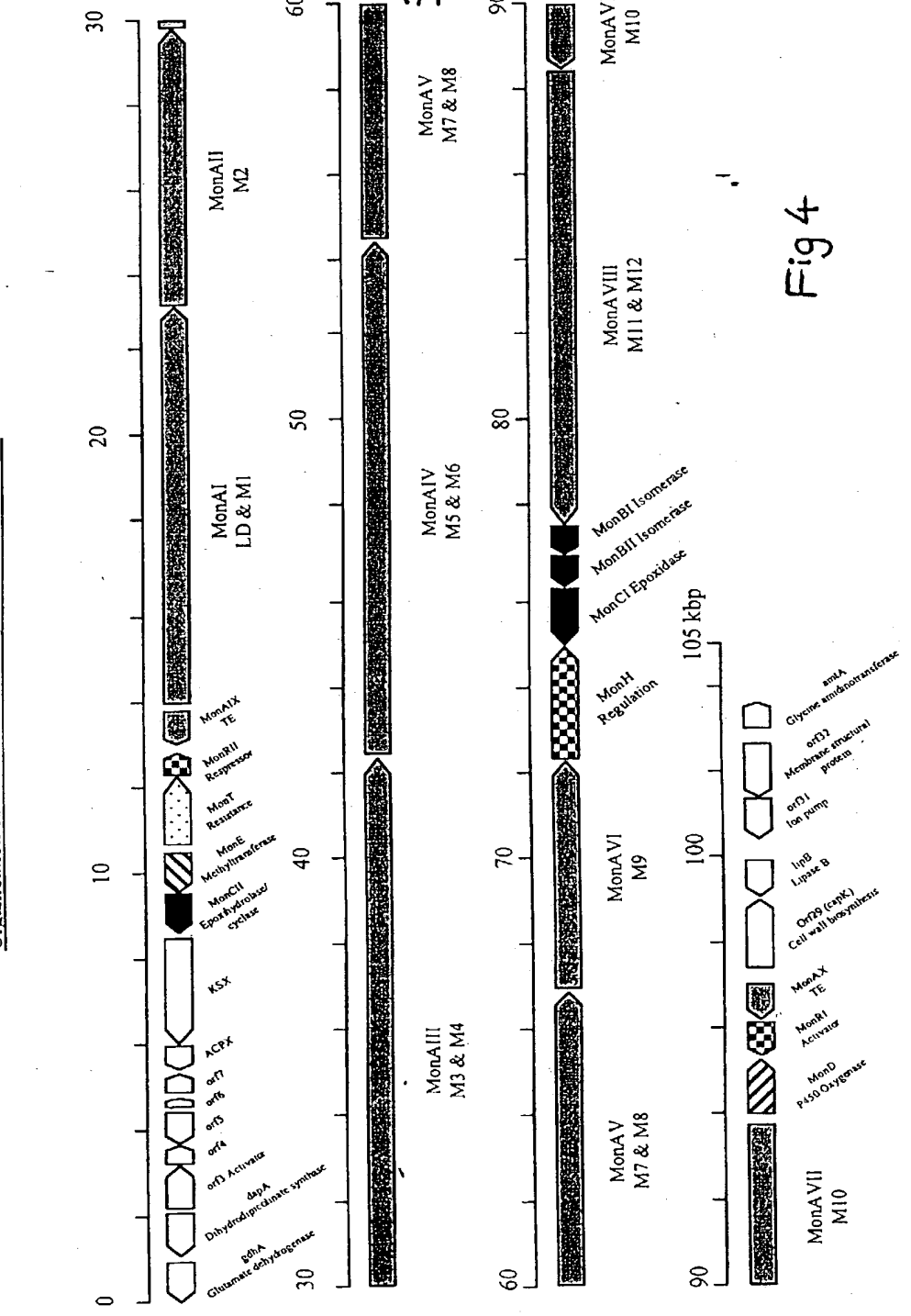
Organisation of the Monensin Biosynthetic Gene Cluster
0
10
20
30
40
50
60
70
80
90
100
105 kbp
gdhA Glutamate dehydrogenase
dapA Dihydrodipicolinate synthase
orf3 Activator
orf4
orf5
orf6
orf7
ACPX
KSX
MonCII Epoxhydrolase/ cyclase
MonE Methyltransferase
MonT Resistance
MonRII Repressor
MonAIX TE
MonAI LD & M1
MonAII M2
MonAIII M3 & M4
MonAIV M5 & M6
MonAV M7 & M8
MonAVI M9
MonAVII M10
MonAVIII M11 & M12
MonC1 Epoxidase
MonBII Isomerase
MonBI Isomerase
MonH Regulation
MonD P450 Oxygenase
MonRI Activator
MonAX TE
Orf29 (cspK) Cell wall biosynthesis
lipB Lipase B
orf31 Ion pump
orf32 Membrane structural protein
amiA Glycine amidinotransferase

Fig 4

SEQUENCE LISTING

```
   1  GATCAGCGCG GTGGCGTCGT CGGCGTCCAG CTCGTTCTGC GTGGCGGACG
  51  GCAGCGCGAT GTCGGCAGGC ACCTCCCAGA CCCGGCGGCC CGGCACGAAG
 101  CGGGCCGAGG CGCCGCGGCG CTGGGCGTAG GTGTCCACGC GGGCGCGTTC
 151  GACCTCCTTG ACCTGCTTGA GGAGGTCCAG GTCGATGCCC TTCTCGTCGA
 201  CGACGTAACC GGAGGAGTCC GAACACGTCA CGGCGTTGGC GCCCAGGGCG
 251  GCGAGCTTCT GGATGGTGTA GATGGCGACG TTCCCGGAGC CGGACACGAC
 301  CGCCGTCCGG CCTTCGAGGG TCTCGCCGCG CTCACGCAGC ATCGCCGCCG
 351  CGAAGAGGAC GTTGCCGTAG CCGGTCGCCT CCGGACGGAT CAGGGAGCCG
 401  CCCCAGTTGC GGCCCTTGCC GGTGAGGACG CCCGCCTCCC AGCGGTTGGT
 451  GATGCGCCGG TACTGACCGA ACAGATAGCC GATCTCCCGG CCGCCGACGC
 501  CGATGTCGCC CGCGGGCACG TCCGTGTGTT CGCCGATGTG CCGGTACAGC
 551  TCCGTCATGA ACGACTGGCA GAAACGCATG ACTTCCGCGT CGCTGCGGCC
 601  GCGCGGGTCG AAGTCGCTGC CGCCCTTGCC GCCGCCGATG CCGAGGCCCG
 651  TCAGCGCGTT CTTGAAGATC TGCTCGAAGC CCAGGAACTT GATGACGCCG
 701  AGGTTCACCG ACGGGTGGAA GCGCAGGCCG CCCTTGTACG GGCCGAGGGC
 751  GCTGTTGAAC TCCACCCGGA AGCCGCGGTT GACCCGCACG CGACCGTGGT
 801  CGTCCTGCCA CGGCACCCGG AAGACGATCT GGCGCTCCGG TTCGCACAGG
 851  CGCTCGATCA GGCCGGCTTC GGCGTACTCG GGGCGAGCCG CGATGACCGG
 901  CGCCAGGGTC TCGAGGACCT CGCGGGCGGC CTGGTGGAAC TCCGGCTGGG
 951  CCGGGTTGCG GTGTTCGATC TCGGTGAGCA GCTGGGAGAG TGCTGTCTTC
1001  TGCGAGAGAG CTGTCTTCGT GTCGGGTCGC GTGGTCAAAG GAGCCCTTTC
1051  TGGCACGGCC GGCGTAGGCG CTCGGCGCCG TTGCCGTGCG CAGGGAGACG
1101  CTCGAGCCGC AAGTATGACG CGCATGTAAA CACAGCGACC AGCCCCCCGG
1151  TCCAGGGAGT GACCACCATG CGAGACCGGG CCACCGGTAG GGCCACCGGT
1201  CCGGCCTGCG GACCCCGTGT CACTTCCGGC TCGCGGCCAG GGGTGCCGCC
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1251 CGGCGGACCG AATCGGCGGA GGCGGCCAGC AGTGGCATGC GGACGGCCGG

1301 GCTGGGAATG CGGTTCTGGG CGTGCAGCAC TCCCTTGATC ACCGTCGGGT

1351 TCGGTTCGGT GAAGAGGGCG GCGGAAAGGC GGGCGAGGTC GGCTCCGAGA

1401 GCGCGGGCGG GTGCGGCGGA GCCGCGTCGC CACAGCGCGA TCATCTCGGC

1451 GTAGTCGGCG GTACGCAGAT TGGCCGACGC CACGATTCCG CCGTGGGCGC

1501 CCGCAGCGAC CAGCGGCGAG AGGACGATGT CGTCACCGCC GAGCACGGCG

1551 AAGCCGGGCA GGGGCGAGTC GAGCAACTCC ATGGTGGTCG GGTCGATCGA

1601 GCCGGTCGCG TGCTTGATGC CGACGACCTC CGGCAGGCGG CCGAGTGCGG

1651 TGATCGTGCC CGCGCCGAGC GTCTGCCCGG TGCGGTAAGG GATGTCGTAC

1701 ACGACCAGGG GGAGGCCGCC GTGCTCGGCC AGCGCGGCGA AATGAGCCAG

1751 GGTCCCCGCT TCCCCGGGGC GGATGTAGGG CGGCGCGGGG ACCAGCGCGG

1801 CGGCGACGTC ACCCCGGGCC GCCAGCTCTC GCAGGGCCGT GATGGCGGTG

1851 GCGGTGTCGT TGGTGCCCAC CCCGACGATG AGCGGTGCCC CGTGTGCCCG

1901 GCACGCGGCC GAGCAGACGC GGATCACCGT CTCTCTCTCC TCGGCGGTCA

1951 GTGTGGCGGC CTCGGCGGTC GTACCGAGGG CGACGAGCCC GGAGGCGCCG

2001 GCCGACAGCG CCTCGTCGGC GAGTCGGGCC AGCGCCTCGG GGGCCAGGCG

2051 CAGATCGTCG GTGAACGGAG TTACCAGGGG GACGTACAGG CCGTTGAAGA

2101 GCGGTTCGGT GGTCGGTTCG AGGCTCGATG CGAGGGTCAT GCTCTTACCC

2151 TGGCCCACGC CACTCGGTAG ATCCATTTCA GATTCCTGCC GTCACACCTA

2201 AGCTGAACTT ATGCTCGATG TCCGTCGCCT CCATCTGCTC CGCGAACTCG

2251 ACCGGCGGGG CACCATCGCC GCCGTGGCCG AAGCGCTGAC CTTCACCGCG

2301 TCCGCCGTCT CCCAGCAGCT CGGCGTGCTG GAGAGGGAGG CGGGCGTGCC

2351 GCTGTTGGAA CGCAGCGGCA GGCGCGTGGT CCTCACGCCC GCAGGACGCT

2401 CCCTCGTCGC ACACGCCGAC GCGGTGCTGA ACCGTCTCGA ACAGGCGGTC

2451 GCCGAGCTGG CGGGCGCACG GGACGGCATC GGCGGGCCGC TGCGCATCGG

2501 GACGTTCCCT TCCGGCGGCC ACACCATCGT CCCCGGCGCG CTGGCCGAAC

```
2551  TGGCCTCTCG TCACCCCGCG TTGGAGCCGA TGGTGCGGGA GATCGACTCC
2601  GCGCGCGTCT CCGACGGTCT GCGGGCCGGT GAGCTGGACG TGGCCCTCGT
2651  ACACGACTAC GACTTCGTAC CCGCGACGCC GGACACGACC GTGGACGAGG
2701  TGCCTCTGCT CGAAGAGCCG ATGTACCTCG TCACCCATGC CGCGGACACT
2751  GCCACGGACT CCGGCTCCGG GAGCACACTG GCAGCGCTGC TCGGGCCCTG
2801  TGCCGAGGTT CCGTGGATCA CGGCGCGGGA CGGCACGACC GGTCACGCGA
2851  TGGCTGTACG CGCCTGTCAG GCCGCCGGGT TCCAGCCCAG GATCCGCCAC
2901  CAGGTCAACG ACTTCCGCAC GGTGCTGGCT CTGGTCGCCG CCGGGCAGGG
2951  GGCCGGGTTC GTGCCGCGGA TGGCCGCCGA GCCGAGCCCC GCGGGCGTGG
3001  TGCTCACGAA GCTGCCGCTG TTCCGTCGCT CGAAGGTCGC GTTCCGTGCG
3051  GGCGGCGGTG CCCATCCGGC GATCGCCGCT TTCGTGGCCG CGGCGACGAC
3101  GGCGGTCGAA CGCATGGCGG GTTCACGAGG CCCGGCCGGC GGCTCTGAGT
3151  GAACCGGCCG ACCGTGGGAA TGTGTGTGCC CTGGGCCGCA CCATTCGTGG
3201  CCTGGTGACG TCCTGGCGAC GTCCTGACGT CCTGATGTCC GAACGAGAAG
3251  GCGATTTTCC GCGATGGCCG ATGACGCGTA CCTGTTCCTC CTCCCCGACC
3301  GGCACCCCCG ACTGGGAGCG GCCCTCGCCG CCGTCGGTGC CTTGGAATGC
3351  ACGGAAACCC CTGCGGTGCA CGCCTGGTTG CAGGCTCATG AGGCCTCCGT
3401  GTCCTCGGAA CAGGTCAGGA TTCTGCCCGC CGATGCCGAG ACACTCATCC
3451  CGAAGGACGC CGAGCGGCTG CCGGTGCCGT TGAGCGAGGA GGAGGCGCTC
3501  AAGGTCGAGC AGGAGTGCGC GCCCCAGACC GTCACGGACA TGGAGAGCGA
3551  ACTGCTCGCG TTCCGGGAGA CGACCCAGGA CTGGCAGGCC CTCGTGCACC
3601  GGGCCCTGAC CGCGGGCATC CCCGCGCAGC GCATCGCCCG GCTGACCGGA
3651  CTCGACCCGG AGGAGATCGG CCGCCTGTAG GCGCTAGCGG CCGCCCAGTG
3701  CGGACACCAG GATGGCGACC GTGACGGTGT TGAAGACGAA GGCGATGACC
3751  GTGTTCGCCG CCACGGTCCG TCGCATGTCG CGTGAGGTGA CGTCGACATC
3801  GGTGGTGCCG AACGTCGTCA TCGCGGCCAG GGCGAAATAG ACGTAGTCGG
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4151  GGACCTGCTC CGGAGCGACG CTCACGAAGA CGGTCATGGT GATGGCGAGG
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4251  AATCCGCACC ACGGCGTCGA TGGGGAGGAC CACTGCCGCG CACGCCGCGA
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5001  CGACTCGCGG GCAGGAAGGG CGCGTTCCGC GGAGTCGGCC GTCGGAGGGG
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5101  CCTGCGCCGC CTTCGTCCGC TTCGTGCTCT GCGGTGGCGG AGTGGGCCTC
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6301  GGCGAGGTGA GGTGGTGGTG CCAGTAGTCG GCGGAGGCGA TGGGGGTGTC
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9251  GTGCGCCGGA CAGGTCGAGG GCGGTGACGG CCGCCACCAG GTCGGTGACG
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17801  GAGCGTGGCC TCGGGCCGCC TGTCGTTCAG CTTCGGCCTT GAGGGGCCCG
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17901  GCGGCGCAGG CGCTGCGGCG CGGCGAGTGC GACCTGGCCC TCGCCGGCGG
17951  CGCCACCGTC CTGGCCACGC CGGGCATGTT CACCGAGTTC TCGCGGCAGC
18001  GGGGCCTGGC CCCCGACGGC CGCTGCAAGC CGTTCGCGGC GGGCGCCGAC
18051  GGCACGGGCT GGGCCGAGGG CGTGGGCCTG GTCCTCCTCG AAAGGCTCTC
18101  CGAGGCCCGG CGCAAGGGGC ACGCCGTCCT CGCGGTGATC CGGGGTTCGG
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19251  GTGGTCGTCG CCGGCGCGCT CACCCTGGAG GACGGCGCCA AGATCGTGGC
19301  CCTGCGCAGC CGGGCGCTGC GTCAGCTCTC GGGCGGGGGC GCCATGGCCT
19351  CCCTCGGGGT GGGCCAGGAA CAGGCAGCCG AACTCGTCGA GGGCCACCCC
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45351  CGCGAGCGGG GACGTACACC TGCTGAGCGG GCGGGTGTCC CGGCAGTCCG
45401  CCGCGTGGCT GGACGACCAC GTCGTGGCGG GCCAGGCCCT GGTGCCCGGC
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45601 CGCGACGTCC GGCTGTTCTC CCGCCCCGAT GACGACGACG CCTTCGCGTC

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46601 TCGACCTCGG CCCCGACGAC ACGCTTGCCG CAGCCATGCA GGCGGCGCAC

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46701 ACTGGTCCGC GCCACGACCG ACCCGACCGC CCCGAACGGG ACACCGGAGG

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47801  TCGACCACCC CACCCCGCAG GCTCTCGCCA CCCACCTGGT GGACCGCTTG
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100651  GACCACCACG TGCGCGGTGA GCACCGGCAT CCCCGAGGTG ACCGTCCAGC
100701  CGTGCAGATC GTGCACGGCG ACCACGCCCC GCTCCTCCAG CAGGTGCCGG
100751  CGCACCTCGC CGAGGTCGAC GTCCTGCGGG GTCGCCTCCA GCAGGACGTG
100801  CAAGGAGTCC CGCAGCAGGC CGTACGCGCG CGGCACGATC AGCAGGCCGA
100851  TGACGATCGA CGCGATCGGG TCGGCGGCCT GCCACCCCGT GAGCAGGATG
100901  ACCAGGCCGC CCACGATCAC CGCGACCGAG CCGAGCGCGT CGCCCAGCAC
100951  CTCCAGGTAC GCGCCCCGCA GATTGAGGCT CTTCTCCTTG GCGTCCCGCA
101001  GCAGCCACAG GCCCACCAGG TTGGCGGCGA GCCCGCCCAG CGCGACCACG
101051  AACATCAGGC CGCCCTTCAC CTCCACCGGC TCGCTGAACC GGCCGATCGC
101101  CGACCACAGG ACCCAGGCGA AGATGACGAC CAGGAGCAGC GCGTTCAGGA
101151  CCGCGGAGAA GATCTCCACG CGGTAGAACC CAAAGGTGCG CCGCGGCGTC
101201  GGCGCCCGCT GGGCGAGGGT GATGGCACCG AGGGCCAGCG AGACGCCGAC
101251  CGCGTCGGTC AGGCTGTGCG CGGCGTCGGC GAGCAGCGCG AGGCTGCCGG
101301  ACAGGAGCGC GCCGACCACC TGGATGACGG TGATCGAGCC GCTGATGCCG
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101351  ATGGTCCACA GCAGGCGCTT GCGGTACGTG CCGCTGAGAG TGCCGCCCGC
101401  CGCCCCGGCG GACGGACCGT GGTCGTGCCC CATGCCCGCG AGTGGACCAC
101451  GGCGGCGCGG CACCCGCCAC CGAGCGGCCG CCGGTCGGCT CAGTGCAGCC
101501  GGGCCTGGGT GGAGGTGTCG CGCTGGTGCG GGATGCCGAG CGGCGGCGGC
101551  AGCTCGCCCT GCTGCACCCT GACCGTGCGC ACGGGGGCGG GGACCCGGAT
101601  GCCCTCGGCG CGGTAACGCT GGTGCAGGCG CTTGATGAAC TCGTGCTTGA
101651  TGCGGTACTG GTCGCTGAAC TCGCCGACGC CGAGGATCAC CGTGAAGCTG
101701  ATCCGCGAGT CGCCGAAGGT GTGGAAGCGG ATCGCCGCCT CGTGGTCGGG
101751  GACCGCGCCG GTGATCTCGG CCATCACCTC GTCCACCACC TCGGTCGTGA
101801  CCTTCTCGAC CTGCTCCAGG TCGCTGTCGT AGCTGACCCC GACCTGCACC
101851  ATGATCGACA GCTCCTGCTC GGGGCGGCTG TAGTTGGTCA TGTTGGTGCC
101901  GGCGAGCTTC GCGTTGGGGA TGATGACGAG GTTGTTGGAG AGCTGGCGGA
101951  CCGTGGTGTT GCGCCAGTTG ATGTCGACGA CGTAGCCCTC CTCCCCGCTG
102001  CTGAGCTGGA TGTAGTCGCC GGGCTGCACG GTCTTCGCGG CGAGGATGTG
102051  CACGCCCGCG AAGAGATTGG CGAGCGTGTC CTGCAGTGCG AGGGCGACCG
102101  CGAGACCTCC CACGCCGAGG GCGGTGAGCA GCGGTGCGAT GGAGATGCCG
102151  AGGGTCTGAA GGACGATGAG GAAGCCCATC GCGAGCACCA CGACGCGGGT
102201  GATGTTCACG AAGATGGTGG CCGATCCGGC CACTCCGGAG CGGGACTGTG
102251  CCACGGCCTT CACCAGGCCG GTGACGATCC GGGCCGCCGT GAGCGTGGCG
102301  GCCAGGATGA GCAGCGCGGT CAGCGTCATG GTGACGTTGC GTCCGGTGCG
102351  CGGCGTGAGC GGCAGCGCGC CCGCCGCGGC GGCGAGCCCG GCGGTGATGG
102401  CCGCGCAGGG CACGAGGGTG CGCAGGGCGT CGACGATGAC GTCGTCACCG
102451  CTCCACCGGG TTTTGCTCGC CCGTTCGCCG AGCCACCTCA GAAGTGCGCG
102501  GAGCAGCAGC CCGGCGACGA CGCCGGCGAC GACCGCGATA CCGGCCACGA
102551  TCCAGTCGTG CAGTGTGAGG GCACGGGTCA TCAGTTCGCT CCCGTCGTAC
102601  GGGGGGAGTG CGCCTGTGTG GGGCGTATGT GATGTGACGT CACCTTGTGA
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102651 TACCTGCTCG ATTCCGGGGA GTGCGGTCAC GCCGGGACGA GAGCTCGGTT

102701 CCGGCGCGGA CGTCATCCTG CCCCATCCGC CCACGGCAGG CGTGCATACC

102751 CCCACCTGGA TCTTCACAGA CCGGCCACGT CTGTCCATGC GCCGATGAGC

102801 GCGCTGCCCG TGGTAAAGCA TTGAGTCAGG CGATTTGGCC ACTCGGCACT

102851 CGGCGGACCG GTCGAGCCGG TCGATCTACG TGAGCGGAGG CGGTTGAGCA

102901 TGGCGTCCAT GTGCAGACCC GGAATGTCAC CCGTCAATTC GCACAACGAG

102951 TGGGATCCGC TGGAGGAGAT CATCGTCGGG CGGCTGGAGG GCGCGACCAT

103001 TCCCTCCAGC CATCCGGTCG TGGCGTGCAA CATCCCGACC TGGGCGGCAC

103051 GGCTGCAGGG TCTCGCCGCC GGGTTCGAGT ATCCGCAGCG GCTGATCGAG

103101 CCGGCGCAGC AGGAGCTCGA CCAGTTCATC GCTCTCCTGC AATCCCTCGA

103151 CGTCACAGTG AGACGGCCGG CGGCCGTCGA CCACAAGCAC CGCTTCGGGA

103201 CCCCCGACTG GCAGTCGCGC GGCTTCTGCA ATTCCTGTCC GCGGGACAGC

103251 ATGCTCGTCG TCGGCGACGA GATCATCGAG ACCCCGATGG CGTGGCCGTG

103301 CCGCTGTTTC GAGACGCACT CGTACCGCGA ACTCCTCAAG GACTACTTCC

103351 GGCGCGGCGC GCGCTGGACG GCGGCGCCGC GCCCCCAGCT CACCGAGGCC

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103451 ATCCTCACCG AGTTCGAGCC GGTGTTCGAC GCGGCGGATT TCGTGCGGGC

103501 GGGCCGCGAC CTGTTCGTGA CGCGGAGCAA CGTCGCCAAC CTGCTGGGCA

103551 TCGAGTGGCT GCGCCGCCAC CTTCGGGCCG GAGTACCGCG TGCCACGAGA

9. MAY. 2002 16:38 MEWBURN ELLIS

DECLARATION, POWER OF ATTORNEY AND POWER TO INSPECT

As a below named inventor, I hereby declare:

that my residence, post office address and citizenship are as stated below next to my name;

that I verily believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural inventors are named below) of the invention entitled: **POLYKETIDES AND THEIR SYNTHESIS** the specification of which [check one(s) applicable]

- X was filed 30 May 2000 as International Patent Application No. PCT/GB00/02072, on which U.S. National Stage Application No. 09/980,217 is based; and/or
- ___ was amended by Amendment filed _____ (if applicable), and/or
- ___ is attached to this Declaration, Power of Attorney and Power to Inspect;

that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above; and

that I acknowledge my duty to disclose information which is material to the examination of this application in accordance with Rule 56(a) [37 C.F.R. §1.56(a)]

CLAIM UNDER 35 U.S.C. §119: I hereby claim foreign priority benefits under 35 U.S.C. §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application of which priority is claimed:

Prior Foreign Application(s) Appln No.	Country	Filing Date Day-Mon-Year	Priority Claimed Yes - No
9912563.5	Great Britain	28-05-1999	Yes

POWER OF ATTORNEY: As inventor, I hereby appoint **DANN, DORFMAN, HERRELL AND SKILLMAN, P.C.** of Philadelphia, Pennsylvania, and the following individual(s) as my attorneys or agents with full power of substitution to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith: **Patrick J. Hagan, Reg. No. 27,643 and Kathleen D. Rigaut, Ph.D., Reg. 43,047.**

POWER TO INSPECT: I hereby give **DANN, DORFMAN, HERRELL AND SKILLMAN, P.C.** of Philadelphia, Pennsylvania or its duly accredited representatives power to inspect and obtain copies of the papers on file relating to this application.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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